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STANDARDIZATION AND CHECKING OF SCHIØTZ TONOMETERS

LIEUTENANT ADOLPH POSNER

MEDICAL CORPS, ARMY OF THE UNITED STATES

Every ophthalmologist has at one time or another doubted the reliability of his tonometer. It is obvious that any measuring device must be based on a standard. Even the length of a yardstick is determined by the Bureau of Standards. Yet there exists the anomalous situation that each ophthalmologist must establish the norms for his own instrument, which may not correspond to any other instrument.

EARLY CHECKING STATIONS

The Schiøtz tonometer, since its introduction in 1905, has gained universal recognition and is accepted as the standard. Since Schiøtz did not patent his tonometer, numerous competitive imitations came on the market, mainly of German manufacture. With them arose the necessity for checking the accuracy of tonometers. Checking stations were organized in Germany by Arnold and Karpow in 1923 [1] and by Comberg in 1928.[2] In 1925 Schiøtz [3] announced a checking station at Oslo, Norway, under his own supervision. In 1935 I [4] organized a checking station at the Herman Knapp Memorial Eye Hospital, which was in operation until the hospital closed in December 1939. This was the only such station in the United States. About two hundred tonometers were received and checked during the five years of its existence.

PRESENT NEED FOR STANDARDIZATION

The need for standardization of tonometers has become even more pressing since the importation of the original Norwegian tonometers and even of the less reliable German-made imitations has of necessity stopped.

The domestically made tonometers, which recently appeared on the market, were not only of inferior workmanship, but actually embodied fundamental defects in construction. To cite only some glaring examples: One manufacturer made the lower end of the plunger convex instead of concave, with the result that it gave readings which were about 12 mm. of mercury too low. Most manufacturers gave no consideration to the weight of the tonometer or of its parts so long as it resembled the original in shape, with the result that no two tonometers gave the same readings.

The most frequent source of discrepancies was found to be in a wrong curvature of the testing block, which naturally led to a faulty zero adjustment of the tonometer.

1. Arnold, H., and Karpow, C.: Ueber die Eichungsverfahren für das Tonometer von Schiötz, Klin. Monatsbl. f. Augenh. **71**:603, 1923.

2. Comberg, W.: Ueber die Kontrolle des Schiötz-Tonometers, Klin. Monatsbl. f. Augenh. **81**:289, 1928.

3. Schiøtz, H.: Tonometry, Brit. J. Ophth. **9**:145, 1925.

4. Posner, A.: A Checking Station for Tonometers, Arch. Ophth. **14**:453 (Sept.) 1935.

This state of affairs was summed up by Harrington and Parsons [5] with the statement that "the slovenliness in construction of Schiötz type tonometers sold at a substantial price in this country is really shocking."

Reese,[6] in a recent editorial, urged the establishment of checking stations in this country. He also admonished ophthalmologists that they "should feel morally compelled to have their tonometers certified by a checking station."

THE PRESENT CHECKING STATION

Since a glaucoma campaign is now being conducted by the Committee on Glaucoma of the National Society for the Prevention of Blindness, it has been thought best to incorporate in this campaign a demonstration checking station for Schiøtz tonometers. Dr. Mark J. Schoenberg, as chairman of this committee, has shown great interest in this phase of the work and has contributed many suggestions.

HISTORY OF THE SCHIØTZ TONOMETER

Principle.—The original description of the tonometer by Schiøtz [7] (1905) referred to it as a compromise between the two types of tonometers then in use, known respectively as the impression and the applanation tonometer. The impression tonometer measured the intraocular pressure by the depth of the impression produced by a constant force, while the applanation tonometer was so named because it measured the amount of force required to flatten a given area of the eyeball. For a detailed historical account of the older as well as the newer tonometers, the reader is referred to the excellent paper by Lloyd.[8] None of the early tonometers were widely used clinically, because they were complicated and inaccurate.

The Schiøtz tonometer indicates on a scale the depth to which a plunger of a given weight will indent the cornea. But there is also provision for changing the weight of the plunger so as to keep the pointer deflection within a certain optimum range on the scale.

Specifications of the Original Tonometer.—In order to visualize the full extent of the problem of standardizing tonometers, it is important to review the various constructional features of the original instrument. Some of the discrepancies noted in certain makes of tonometers can be accounted for by a faulty interpretation of the measurements given by Schiøtz. As a matter of fact, Schiøtz himself has revised his specifications at various times, and it is only by a careful analysis of his publications and of his numerous experiments that the changes can be understood and coordinated.

By referring to table 1, one notes that the diameter of the foot plate, which was originally given as 9 mm., was subsequently changed to 10.2 mm., and the area of the foot plate was thus established at 84 sq. mm.

The weight of the plunger, including the 5.5 weight, lever and pointer, is given as 5.5 Gm., but it is not stated whether this figure includes friction or whether it represents the weight of the unassembled parts. If the plunger supports the lever in its center of gravity, as it should, the two weights should be the same except for the effect of friction. By actual measurements it was found that the unassembled weight is slightly lower than 5.5 Gm. and that assembled the parts weigh slightly more, the difference varying with certain factors which will be dealt with later.

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5. Harrington, D. O., and Parsons, A. H.: Tonometric Standardization, Arch. Ophth. **26**:859 (Nov.) 1941.

6. Reese, A. B.: Standardizing and Checking Tonometers, Am. J. Ophth. **25**:478, 1942.

7. Schiøtz, H.: Ein neuer Tonometer, Arch. f. Augenh. **52**:401, 1905.

8. Lloyd, R. I.: Tonometry and Various Instruments Employed in Its Practice, Am. J. Ophth. **13**:396 and 496, 1930.

The weight of the remainder of the tonometer minus the handle is given as "approximately 10 Gm." (1909) [9] or 10.1 Gm. (1920).[10] In the original paper (1905) [7] Schiøtz gave the weight as "about 12 Gm.," but this includes the lever and pointer. Through a misunderstanding, Friedenwald [11] and later Harrington and Parsons [5] adopted 12 Gm., instead of the former figure of 10 Gm., as the standard weight without lever and pointer.

This difference of 2 Gm. is a minor source of error and would account for a difference of between 0.4 and 0.1 of a scale division (Schiøtz, 1920 [10]). By weighing several original Schiøtz tonometers, it was found that the weight averaged about 11 Gm. Therefore, this figure was accepted as the standard.

One final item must be considered, and this, by the way, is the most frequent cause of faulty adjustment of tonometers. I am referring to the testing block which accompanies each tonometer.

In the first publication, Schiøtz merely spoke of the testing block as a "convex model," without stating the amount of convexity. However, he must have assumed that its radius of curvature was the same as that of the foot plate, namely, 15 mm., for in 1909 [9] he wrote as follows:

> In the earlier tonometers the foot plate was made independently of the test block. Later, these two parts were ground together in order to insure a perfect fit. However, these tonometers gave somewhat greater deflections near the zero region. . . . Accurate measurements of the foot plate and test block of my tonometer with which all measurements were being made, the Javal-Schiøtz ophthalmometer being used, showed that the concavity of the foot plate had a radius of curvature of 15 mm., while the convexity of the test block had a radius of 18 to 20 mm. . . . Since all calculations and curves were based on measurements made with my instrument, I had the instruments so adjusted that the surface of the test block was slightly less convex than the foot plate was concave.

This rather indefinite statement was further amplified in 1920, when Schiøtz [10] wrote:

> I presume that everyone has noticed the facet or small flat area in the convex surface of the model. . . . The "model" belonging to the standard tonometer, with which all measurements for the graphs were made, was found to have a slightly longer radius of curvature than the corresponding concavity of the foot, the difference being such as to cause the index to point one millimetre beyond the zero line when an exactly fitting model [of 15 mm. radius of curvature] was used.

It was found by experiment that a tonometer when placed on a convex block of 18 mm. radius of curvature will give a pointer deflection which is at least 3 mm. more than that obtained on a sphere of 15 mm. radius, and not a 1 mm. difference, as stated by Schiøtz.[10] By calculation and experiment, the radius of curvature necessary to attain the latter criterion was found to be 16 mm. In other words, instead of the top of a 15 mm. block being flattened, the radius of curvature is made 16 mm., and a tonometer adjusted to read "0" on such a block will read "— 1" on a 15 mm. block. One may ask oneself the question: Why did Schiøtz find his block to have a radius of curvature of "18 to 20 mm." ? The answer may be found in the method of measurement he used. The ophthalmometer covers only a small area, and it is possible that the convex surface of the testing block was aspherical, the central portion, the curvature of which he measured, being flatter than the peripheral portion.

Later Models of Schiøtz Tonometers.—Without changing any of the basic specifications, which would have necessitated a change in the graphs, Schiøtz modified his tonometer in 1925 [3] in order to simplify the procedure of changing the

9. Schiøtz, H.: Tonometrie, Arch. f. Augenh. **62**:317, 1909.
10. Schiøtz, H.: Tonometry, Brit. J. Ophth. **4**:201 and 249, 1920.
11. Friedenwald, J. S.: Contribution to the Theory and Practice of Tonometry, Am. J. Ophth. **20**:985, 1937.

weights. In the 1925 model the 5.5 weight remains permanently screwed on, while additional disks are superimposed to increase the weight of the plunger to 7.5 and 10 Gm., respectively. Other improvements are a double post, instead of a single one, to support the scale, and a circular gutter in the foot plate around the lower end of the plunger, to minimize the capillary attraction of tears, which tends to increase friction.

At this time, Schiøtz published also his new corrected graphs for translating the readings into millimeters of mercury. However, these graphs are in no way

TABLE 1.—*Specifications of the Schiøtz Tonometer*

	Schiøtz' Specifications		Posner's Measurements		
	Measurements Given by Schiøtz	Reference	Old Model (No. 1) Tonometer	New Model (No. 869) Tonometer	Tonometer Adopted as Standard
1. Short arm of lever (plunger to fulcrum)	4 mm.	Schiøtz [7]	4 mm.	4 mm.	4 mm.
2. Long arm of lever (length of pointer)	80 mm.	Schiøtz [7]	80 mm.	80 mm.	80 mm.
3. Radius of curvature of foot plate	15 mm.	Schiøtz [7]	15 mm.	15 mm.	15 mm.
4. Radius of curvature of concave lower end of plunger	15 mm.	Schiøtz [7]	15 mm.	15 mm.	15 mm.
5. Diameter of plunger.....	3 mm.	Schiøtz [7]	3 mm.	3 mm.	3 mm.
6. Diameter of foot plate.....	9 mm. 10.2 mm.	Schiøtz [7] Schiøtz [9]	10.2 mm.	9.7 mm.	10.3 mm.
7. Area of foot plate and plunger	81.7 sq. mm.* 84 sq. mm.	Schiøtz [9] Schiøtz [10]			
8. Weight of plunger, lever, pointer and 5.5. weight (this represents the force which dimples the cornea)	Dismantled Not stated Assembled (includes † 5.5 Gm. friction)	..... Schiøtz [7]	5.12 Gm. 5.50 Gm.	5.35 Gm. 5.81 Gm.	5.40 Gm. 5.50-5.70 Gm.
9. Weight of tonometer without handle, lever, pointer, plunger, weight	"Approximately 10 Gm." 10.1 Gm.	Schiøtz [9] Schiøtz [10]	11.35 Gm.	11.10 Gm.	11.0 Gm.
10. Weight of tonometer "without weight and plunger" (apparently includes lever ‡ and pointer)	"Approximately 12 Gm."	Schiøtz [7]	12.34 Gm.	12.65 Gm.	
11. Weight of lever with pointer	Not stated	.....	0.99 Gm.	1.55 Gm.	Is included in item 8
12. Radius of curvature of corneal block supplied with tonometer	18 to 20 mm. radius § Slightly greater than 15 mm. so as to read —1 when placed on a 15 mm. sphere	Schiøtz [9] Schiøtz [10]	15 mm., with flattened central area of 3.5 mm. diameter	15 mm.	16 mm.

* In 1909 Schiøtz gave 81.7 sq. mm. as corresponding to a diameter of 10.2 mm. This is inaccurate; 84 sq. mm. is the correct area. In 1920 Schiøtz corrected this figure.

† The plunger should balance the lever at the center of gravity, so that the entire weight of the lever may rest on the tip of the plunger. However, this usually does not hold true for all positions of the pointer.

‡ This specification as to the weight of the tonometer (12 Gm.) was the only one mentioned in the original paper (1905). Since it was somewhat ambiguously stated, it has given rise to misinterpretations. For instance, Friedenwald erroneously thought it referred to the weight of the tonometer without plunger, weight and lever arm. In a later communication [9] Schiøtz gave the weight not including the lever arm as about 10 Gm. However, by careful weighing of several original tonometers, it was found that 11 Gm. more closely approximates the average weight.

§ This radius of curvature is incorrect. A radius of curvature of 18 mm. gives a deflection 3 mm. greater than a sphere of 15 mm. radius. Since only a 1 mm. difference is desired, the radius of curvature should be 16 mm. The error may be accounted for by the fact that Schiøtz used an ophthalmometer which measured only the curvature of the central, flattened portion of the surface.

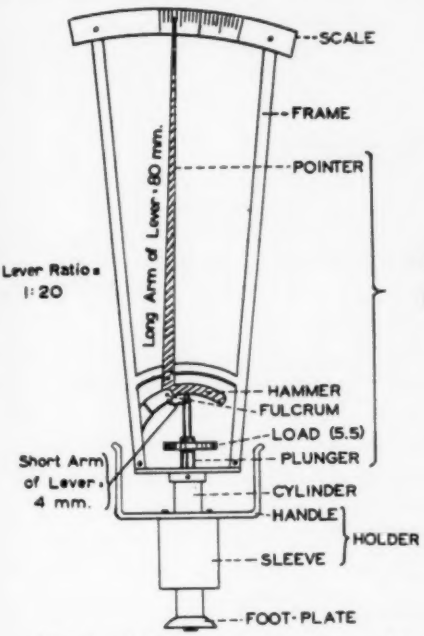
dependent on the use of the new model tonometer, as some ophthalmologists imagine, but apply equally to the original model. They give mercury equivalents approximately 4 to 5 mm. higher than those of the old graphs. They were arrived at by an improved experimental technic after Priestley Smith [12] and McLean [13] had called attention to the fact that the values given by Schiøtz were too low.

12. Smith, P.: Limitations of the Tonometer, Ophth. Rev. **34**:65, 1915.

13. McLean, W.: Further Experimental Studies in Intraocular Pressure and Tonometry, Brit. J. Ophth. **3**:385, 1919.

It may be permissible at this point to clear up another misconception. In 1926[14] Schiøtz introduced the X tonometer. This is a tonometer with a convex plunger instead of the concave plunger of the standard tonometer. It has certain advantages, of which it is necessary to consider now only the fact that no weights (not even the 5.5 disk) are used with it, the plunger alone, which is held in place by means of a clip, supplying sufficient weight (4 Gm.). Only one curve is required to cover the entire range of intraocular pressures. Of course this curve is entirely different from any of the curves used with the tonometer having a concave plunger.

Some of the American manufacturers, thinking that the convex plunger is merely an improvement of the old tonometer, designed their tonometers with a convex plunger but made the mistake of supplying with it the standard graphs applicable only to the tonometer with a concave plunger, as well as the three additional weights.



SPECIFICATIONS OF THE STANDARD TONOMETER

Weight of plunger, load (5.5), pointer and hammer	5.5 Gm.
Weight of tonometer without holder	16.5 Gm.
Diameter of foot plate	10.2 mm.
Diameter of plunger	3 mm.
Radius of curvature of foot plate	15 mm.
Radius of curvature of plunger (concave)	15 mm.
Radius of curvature of testing block	16 mm.
Length of long arm of lever	80 mm.
Length of short arm of lever	4 mm.
Lever ratio	1:20
Scale	in millimeters

THE TWO MOST COMMON DEFECTS ARE: 1. WRONG CURVATURE OF TESTING BLOCK 2. INCORRECT LEVER RATIO

Fig. 1.—Diagram of the new model Schiøtz tonometer together with the specifications accepted as standard.

The ophthalmologist who is not aware of this error is at a loss to explain the enormous discrepancies between the readings of his old tonometer and those of the one he has just purchased.

It is significant of the general lack of accurate information to find a misstatement based on a similar misconception in the generally authoritative textbook of ophthalmology by Duke-Elder:[15]

> In the latest Schiötz instrument (1926) a plunger with a convex surface rests upon the cornea, the amount of indentation being transmitted to a lever reading on a scale. The plunger is weighted by one of three weights (5.5, 7.5 and 10 grams). . . .

Again the impression is conveyed that the X tonometer is simply an improved model of the original.

14. Schiøtz, H.: Tonometrie: Tonometer mit konvexem Zapfen, Acta ophth. **4**:1, 1926; Tonometry: Tonometer with Convex Plunger, Brit. J. Ophth. **11**:116, 1927.

15. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1191.

EQUIPMENT OF CHECKING STATION

The first prerequisite for checking on tonometers is a reliable standard, which must adhere strictly to Schiøtz' specifications and when these are ambiguous to whatever specifications are adopted as standard. A set of specifications was drawn up, and, since even the original Norwegian tonometers do not fully conform to these standards, a tonometer had to be built especially for the purpose.

The J. Sklar Manufacturing Company cooperated in making up the standard tonometer. The measurements adopted as standard are as follows:

1. The combined weight of plunger, 5.5 weight, hammer and pointer (the impression-producing unit) including friction:	
(*a*) with pointer at 0, or left end of scale	5.5 Gm.
(*b*) with pointer at 20, or right end of scale, not to exceed	5.8 Gm.
2. Weight of entire tonometer (without the handle), including friction	16.5 Gm.
3. Weight of additional loads:	
(*a*) 7.5 disk	2.0 Gm.
(*b*) 10.0 disk	4.5 Gm.
4. Friction between handle and tonometer, determined by difference of minimum and maximum weight, not to exceed	0.2 Gm.
5. Diameter of plunger	3.0 mm.
6. Diameter of foot plate	10.2 mm.
7. Distance from fulcrum to scale (long arm of lever)	80.0 mm.
8. Radius of curvature of plunger	15.0 mm., concave
9. Radius of curvature of foot plate	15.0 mm.
10. Radius of curvature of testing block	16.0 mm.
11. Deflections of pointer on micrometer block at various adjustments:	
(*a*) at 0 0	(*d*) at 15 15
(*b*) at 5 5	(*e*) at 20 20
(*c*) at 10 10	
12. Calculated lever ratio, values from 0 to 10 only being used	1:20
13. Deflection of pointer on a disk of 15 mm. radius	—1
14. Deflection of pointer on testing block of 16 mm. radius of curvature	0

A tonometer submitted for checking is measured with regard to the various specifications listed, after which it is tested on a rubber membrane connected with a manometer (or on a patient if one is available) to determine whether its readings compare with those of the standard tonometer.

Any discrepancies found must be evaluated as to their importance, that is, as to their possible effect on the reliability of the readings. It should be borne in mind, however, that several slight discrepancies may add up to an appreciable error in the actual use of the instrument. This can be uncovered through the test on the manometer.

It must be stressed at the outset that the test with the manometer is of secondary importance, since it is not intended to calibrate the instrument. It serves merely as a convenient substitute for use of a human eye, and conclusions can be drawn from it only if the construction of the tonometer tested is similar to that of the one used as a standard.

Since the rubber drum is not in a true sense a replica of the human eyeball, one cannot use it to compare, for instance, a McLean tonometer with a Schiøtz tonometer. Such comparisons were attempted a few times, with disappointing results.

The remainder of the equipment for checking tonometers is as follows:

1. A ruler divided in half-millimeters.

2. A micrometer gage. (The A. D. Leveridge millimeter gage, used by jewelers, was adopted as an accurate instrument which is simple to operate.)

3. A set of three metal disks of the following radiuses: 15 mm., 14 mm. and 16 mm.

4. A set of three metal rings with the following inside radiuses: 16 mm., 14 mm. and 18 mm.

5. A micrometer block having a convex upper surface of 15 mm. radius of curvature, a movable core of 3.1 mm. diameter and a 1 mm. thread. The circumference is divided into twenty equal parts, each representing 0.05 mm. of plunger movement and hence one division on the tonometer scale. The zero line on the micrometer block represents a drop of 0.05 mm., so that the tonometer will read "0" on it.

6. A pharmaceutical balance of the torsion type. This balance is so constructed that the pans move vertically. A vertical pin is mounted in the center of one of the pans to support the plunger of the tonometer.

7. A set of gram weights (1 to 10 Gm., no fractions).

8. An adjustable stand for supporting the tonometer in a vertical position. A microscope base was utilized for this purpose. A horizontal arm with a ring to hold the tonometer was attached to the vertical post, so that it could be raised and lowered by means of the rack and pinion of the microscope.

PROCEDURE OF CHECKING TONOMETERS

The checking of a tonometer involves the determination of the various measurements and specifications enumerated. The steps followed are evident from table 2, which is a copy of the actual record used by the checking station. Hence, only some of the essential points in the technic and in the interpretation of findings will be discussed under this heading.

In order to weigh the plunger-lever mechanism, the tonometer is clamped vertically in the arm of the stand and lowered so that the plunger is pushed up by the vertical pin attached to one pan and the pointer of the tonometer is in the "O" position.

The procedure is then repeated with the pointer in the "20" position.

In the first position the weight of the pointer is at least partially taken up by the fulcrum, while in the second position it is entirely supported by the plunger, thus increasing the weight of the latter. This increase in weight is partly compensated by the lessened mechanical advantage of the free end of the hammer, which comes to lie closer to the fulcrum as it rotates downward. In the older models of tonometer, in which the end of the hammer is bulbous, this compensation is more nearly perfect than in the new models, in which the thickness of the hammer is practically uniform throughout its length. The difference between the two readings need not exceed 0.2 Gm. but even if it does slightly exceed this figure the fluctuation is not very important, since to get accurate readings, according to Schiøtz, only a small portion of the scale should be used, namely that between "2" and "6."

In order to minimize this fluctuation, the pointer should be as light as possible. The pointer on one make of tonometer was so heavy that the fluctuation was over 1 Gm., and this was reflected in the readings which the tonometer gave in actual clinical use.

The weight of the entire tonometer is obtained by lowering the instrument still further, till it rests unsupported on the flat part of the pan. The weight of 16.5 Gm. was adopted as standard because most original tonometers weigh that much, even though Schiøtz' specifications call for 15.6 Gm. A difference of 1 Gm. influences the reading very slightly, not more than two tenths of one division.

The additional loads should weigh the difference between 5.5 Gm. and the number marked on the load. Thus the 7.5 load should weigh 2 Gm. and the 10 load 4.5 Gm. It is not necessary to weigh each load on the tonometer, because for practical purposes it may be assumed that the effect of friction is the same no matter what weight is used.

With the older models, in which each load screws on separately, one can either weigh the plunger with each separate load attached to it or use this short cut: The plunger and lever having been weighed with the 5.5 load, this load is removed and placed on the pan where the gram weights are. Then the 7.5 and 10 loads are weighed individually, the result being the weight of the difference between the 5.5 and each of the two other loads.

TABLE 2.—*Tonometer Checking Station—Record of Checking*

Schiøtz tonometer—Model: old..... new..... No.....
make..... number.....
other identifying marks.....
Received from.....
Date rec'd..... Report sent..... Checked by.....

	Correct	Wrong
Weight of plunger (1) at 0.....		
(2) at 20.....		
Weight of tonometer.....		
Friction (approximate).....		
Weight of loads 7.5 Gm.....		
10.0 Gm.....		
Diameter: Foot plate.....		
Plunger.....		
Curvature: Foot plate.....		
Plunger.....		
Testing block.....		
Reading on 15 mm. disk.....		
on 16 mm. block.....		
on own block.....		

Determination of lever ratio:

	at	0	5	10	15	20
On micrometer block.....						
Standard tonometer reads.....		0	5	10	15	20
This tonometer reads.....		..	..	..	..	..

Calculated lever ratio (with readings at 0, 5 and 10 only)

	5.5 load	7.5 load
On manometer, at 30 mm. Hg.....		
Standard tonometer reads.....		
This tonometer reads.....		

Remarks:.....
.....

Note:
Tonometer should read..... on testing block.....
on plate glass surface.....

Signed:.....
Director of Tonometer Checking Station

To estimate the friction between the handle and the tonometer proper, the weights are increased gradually until the balance shows no deflection; then weights are again added until the deflection is in the opposite direction. The difference between the minimum and the maximum weight represents the friction in the tonometer.

The following procedure is used in estimating the friction between the plunger and the cylinder: The tonometer is held horizontal and then slowly inclined, the angle sufficient to cause the plunger to slide either up or down along the cylinder being noted. In a well polished instrument this angle is very small, even less than 5 degrees.

There is a third source of friction and one which is difficult to measure. It is caused by the sliding of the upper end of the plunger along the under surface of the hammer. This excursion is less than 1 mm. in extent, but the friction it creates

may be considerable, especially in old tonometers in which the under surface of the hammer has been pitted by continued use.

This source of error, which has been emphasized by Friedenwald,[16] can be obviated by a modification in construction. This will be treated in another paper now in preparation.

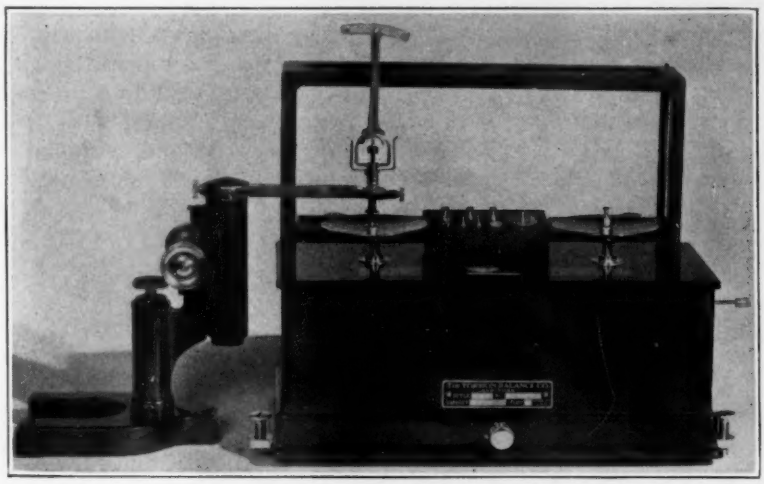


Fig. 2.—Weighing the tonometer. The tonometer is lowered until a pin which projects from the pan of the torsion balance supports the plunger. This gives the weight of the impression unit. When the entire tonometer rests on the pan the reading represents the weight of the entire tonometer.

Fig. 3.—Measuring the diameter of the plunger. The A. D. Leveridge millimeter gage quickly measures this, as well as the diameter of the foot plate, accurately to 0.05 mm.

The diameters of foot plate and plunger are readily measured with the Leveridge micrometer gage or any other type of micrometer.

The curvature of the lower surfaces of the foot plate and plunger are measured by pressing firmly against them a disk of the standard radius. If the disk fits

16. Friedenwald, J. S., in discussion on Harrington and Parsons.[5]

perfectly, the curvatures are normal. Slightly larger and smaller disks are provided to determine the approximate deviation from the standard, whether slight or considerable.

Similar disks with the centers cut out to give rings of known radiuses are used to measure the testing block.

As mentioned, the standard testing block has a radius of curvature of 16 mm. The testing blocks supplied with tonometers have been found to have various shapes. Some are entirely aspherical, and others are 15 mm. curves with a central facet. A testing block of any shape can be used so long as the tonometer will give the same reading on it as on a standard 16 mm. block. According to Schiøtz' own specifications, a tonometer is properly adjusted on its testing block if it gives a deflection of "— 1" when placed on a sphere or disk of 15 mm. radius of curvature. For this reason, this additional check is used.

Fig. 4.—Measuring the radius of curvature of the foot plate. Three disks of known radiuses are sufficient for rapid estimation. The 15 mm. disk should give a good fit.

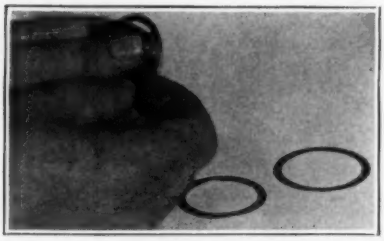


Fig. 5.—Measuring the radius of curvature of the testing block. Three rings of 15, 16 and 18 mm. inner radiuses are sufficient. The 16 mm. ring should fit perfectly when placed on the block.

The mechanical principle of the tonometer lies in the lever mechanism, which magnifies the downward movement of the plunger twenty times. To accomplish this, the short arm of the lever, formed by the distance between the fulcrum and the plunger, is 4 mm., while the distance between the fulcrum and the scale (the long arm of the lever) is 80 mm.

It is easy to measure the latter, but it is next to impossible to measure accurately the short arm of the lever, especially since the two points of reference are not in the same plane and the effect of parallax has to be taken into account. Attempts at indirect measurement have been given up in favor of the direct measurement of the lever ratio. By means of the micrometer block, the plunger is permitted to drop a known distance by lowering of the central core in the block by

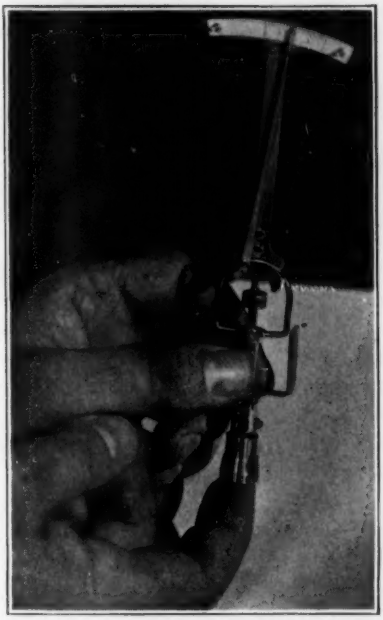


Fig. 6.—Determination of the lever ratio. The tonometer is placed on a micrometer block which has a curved surface of 15 mm. radius. The depth of a central 3 mm. depression, into which the plunger of the tonometer fits, can be changed by known amounts and can be compared with the corresponding deflection of the pointer.

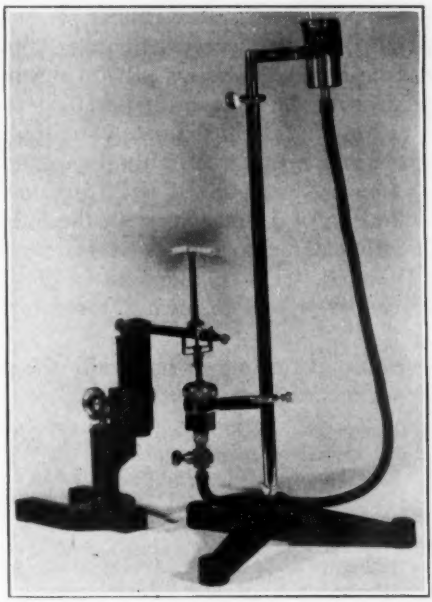


Fig. 7.—Manometric calibration. The tonometer is compared with a standard on a curved rubber drum communicating with a water manometer. The pressure behind the rubber drum can be varied by changing the level of the manometer.

a definite amount. Several readings are taken along the scale, but only the left half of the scale is considered in the calculation of the lever ratio, which is carried out as follows:

$$\text{Lever ratio} \quad \frac{1}{(\text{Reading at } 10) - (\text{Reading at } 0) \times 2}$$

Example: Reading at 0 = 1
Reading at 10 = 13.5

$$\text{Lever ratio} = \frac{1}{(13.5 - 1) \times 2} = \frac{1}{25}$$

In the example the lever ratio is 1 : 25 instead of 1 : 20. After the tonometer has been adjusted to read "0" on a 16 mm. testing block it will still give readings which are too high (i. e. pressures too low). For instance, instead of a reading of "4," it will give a reading of "5." The correction can be made by multiplying each reading by the factor 0.8. Better still, the scale can be so changed that the divisions are not 1 mm. but 1.25 mm. apart. A third, more difficult procedure would be to bend the tonometer in such a way as to increase the short arm of the lever sufficiently to give the standard readings.

To have a simple check on the permanency of a given lever ratio after it has once been established, the readings at two points on the scale have to be known. One point is the "0" point obtained on the testing block. For the other point on the scale, one may use a flat glass plate which is always readily available. On such a plate the reading will be about fourteen divisions, since the height of the segment of a sphere formed by the foot plate above and the glass plate below is about 0.7 mm. But whatever the reading may be, once determined it should always remain the same if the tonometer is to function uniformly.

The manometric check-up serves, as has been stated, merely to compare the readings of any tonometer with the standard tonometer. Only similarly built tonometers may be compared in this way, since the rubber membrane does not represent a true replica of the human eye and therefore findings obtained with it have only relative value and cannot be applied unreservedly to the human eye. Since only one or two readings need be taken, it is most practical to make the comparison at that pressure which corresponds approximately to the upper limit of normal intraocular pressure. The water manometer is therefore so adjusted that a reading of 30 mm. of mercury (Schiøtz) is obtained with the standard tonometer. This would mean a pointer deflection of 3 divisions with the 5.5 load and of 5 divisions with the 7.5 load. The tonometer to be tested is then placed on the rubber drum, and its reading is noted. The manometer is closed by shutting off the connection between the metal eye and the water reservoir, before the tonometer is placed on the drum.

An example will serve to explain more graphically the procedure followed and the conclusions drawn from the various tests:

Old style Schiøtz type tonometer
No name of manufacturer given; no serial number
Weight of plunger, 5.5 load, hammer, pointed at "0" = 5.43 Gm.
at "20" = 5.8 Gm.
Weight of entire tonometer without holder = 16.5 Gm.
Friction = 1 +, or about 0.4 Gm.
Weight of 7.5 load = 1.97 Gm. } Difference over 5.5 Gm. load
10.0 load = 4.48 Gm. }
Diameter of foot plate, 10.15 mm.
Diameter of plunger, 3.03 mm.
On 15 mm. disk, reading = — 1
On 16 mm. block, reading = 0
On own block, reading = 0

Readings on micrometer block:

at 0 = 0 at 5 = 4 at 10 = 8.5	Hence lever ratio is not 1 : 20 but 1 : 17 in lower portion of
at 15 = 13.5 at 20 = 18.5	the scale, which is the important portion

Radius of curvature of foot plate = 15.5 mm. (should be 15!)
Radius of curvature of testing block = 16 + mm.
Lower end of plunger: concave (edges nicked and irregular)
Comparison on rubber membrane with manometer at 30 mm. of mercury (Schiøtz)
Standard tonometer with 7.5 weight..... 5 divisions
This tonometer..... 4 divisions

Remarks: Taking into account the differences in the lever ratio, the reading of 4 on this tonometer corresponds to the reading of 5 on the standard. The scale of this tonometer can be recalibrated so as to correspond with its lever ratio.

The lower surface of the plunger should be polished and its edge smoothed down.

From the foregoing it is evident that the work of the checking station is of a distinctly practical nature. It is intended to achieve uniformity in calibration among all Schiøtz tonometers now in use.

The tonometer is of great clinical value, even though it must be admitted that it is not a scientifically perfect instrument. Research is now being conducted with the object of eliminating most of its defects and of constructing a more sensitive and more accurate tonometer, which would enhance its value in the study of the physiology and pathology of the eye.

In the course of this work the following sources of error have been found to be the most important in affecting the accuracy of the instrument:

1. Wrong curvature of the testing block.
2. Incorrect lever ratio.
3. A flattened, or even convex, lower end of the plunger.

SUMMARY

The lack of uniformity among Schiøtz tonometers of various manufactures, and even among those of the same manufacture, has made it imperative to set up standard specifications and to organize a checking station to test tonometers now in use and certify new tonometers as to accuracy of construction and performance. Such a checking station is now in operation and is temporarily located at the offices of the National Society for the Prevention of Blindness, 1790 Broadway, New York.

246 West End Avenue.

CORNEAL TRANSPLANTATION

RICHARD A. PERRITT, M.D.
CHICAGO

The purpose of this paper is to present the evolutionary stages through which my work on corneal transplantation in cooperation with Dr. Sanford R. Gifford has passed. Certain technics have been modified and others discarded.

At first an apron conjunctival flap was used, according to the Filatov [1] technic. A review of the Russian and French literature reveals that Filatov has modified and changed his trephine operation [2] several times and completely discarded his prophylactic spatula.

The conjunctival flap was discarded because:

1. Occasionally the edges of the transplant had a tendency to protrude.

2. On one occasion the corneal disk completely slipped away from the corneal opening. Later a tattooing of the slightly staphylomatous scar yielded satisfactory results.

3. A subsequent increase in tension might be produced by the connective tissue developing around the limbus after the dissection of the conjunctiva.

4. In some cases there was so much conjunctival scar tissue that it was difficult to obtain a conjunctival flap.

The Thomas technic [3] was modified so that the corneal disk of the recipient and that of the donor eye were similar in size.

Beveling was produced in the recipient eye at approximately a 25 degree angle, but *the donor cornea was not beveled.* The significance of this lies in the fact that when beveling of both the donor cornea and the recipient eye is performed, a curling of the endothelium results, together with a gradual reformation of scar tissue in the interstices (fig. 1 *A*).

Read before the Chicago Ophthalmological Society Nov. 17, 1942.

From the Department of Ophthalmology, Northwestern University Medical School, with the cooperation of Dr. Sanford R. Gifford, and the Department of Ophthalmology, Wesley Memorial Hospital.

1. Filatov, V. P.: (*a*) Total Transplantation of Cornea, Sovet. vestnik oftal. **2**:217, 1933; (*b*) La cornée de cadavre comme matériel de transplantation, Ann. d'ocul. **171**:721, 1934; (*c*) Sobre la técnica de la operación de la transplantación parcial penetrante de la córnea, Arch. de oftal. hispano-am. **34**:457, 1934; (*d*) New Trephine for Partial Transplantation of Cornea, Sovet. vestnik oftal. **4**:12, 1934; (*e*) Use of Cornea from Cadaver as Transplantation Material, ibid. **4**:222, 1934; (*f*) Technic of Transplantation of Cornea; Filatov-Martsinkovskiy's Hermetic Trephine, ibid. **8**:159, 1936.

2. Wassermann, I.: On the Technique of Leucoma Exsection with New Modification of Trephine FM-III, Kiev, U. S. S. R. Academy of Sciences Press, 1938, p. 160. Filatov.[1f]

3. Thomas, J. W. T.: Transplantation of the Cornea: A Preliminary Report of a Series of Experiments on Rabbits, Together with a Demonstration of Four Rabbits with Clear Corneal Grafts, Tr. Ophth. Soc. U. Kingdom **50**:127, 1930; Successful Grafting of the Cornea in Rabbits, Lancet **1**:335, 1931; Microscopic Appearances of Corneal Grafts, Brit. J. Ophth. **17**:529, 1933; The Technique of Corneal Transplantation as Applied in a Series of Cases, Tr. Ophth. Soc. U. Kingdom **55**:373, 1935; Experimental Heterogenous Corneal Grafts, ibid. **56**:97, 1936; The Results of Corneal Transplantation, Brit. M. J. **1**:114, 1937; Clinical Record and Histology of Two Successful Corneal Grafts in Man, Tr. Ophth. Soc. U. Kingdom **55**:114, 1935; The Clinical and Microscopic Appearances of Experimental Grafts of Scleral Tissue on to Rabbits' Corneae, ibid. (pt. 1) **57**:198, 1937.

An absence of curling of the endothelium is one of the main preventives of subsequent opacities (fig. 1 *B*). The continuity and functional integrity of both the epithelium and the endothelium are of the greatest importance both for the maintenance of respiration and for the control of fluid transfer in the corneal tissue.

The Castroviejo [4] method was reduced to its simplest terms. The Castroviejo trephine has been accepted and employed. The central corneal suture used has a threefold purpose:

1. It serves to keep the leukomatous portion away from the lens capsule.
2. It initiates the beveling process.

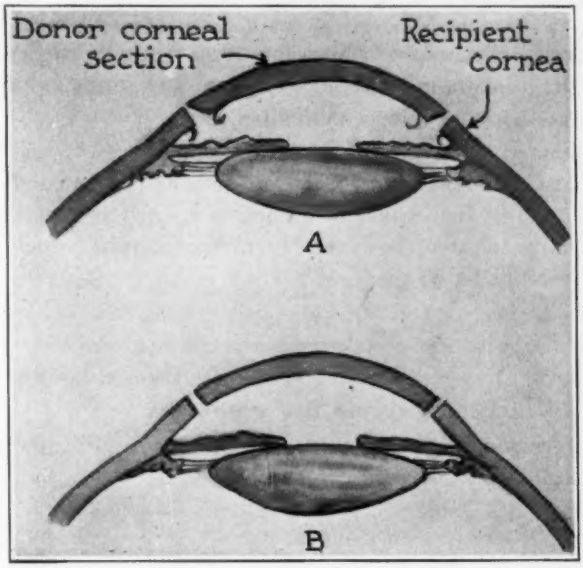


Fig. 1.—*A*, endothelial curling when both the donor and the recipient cornea are beveled. *B*, absence of endothelial curling when only the recipient cornea is beveled.

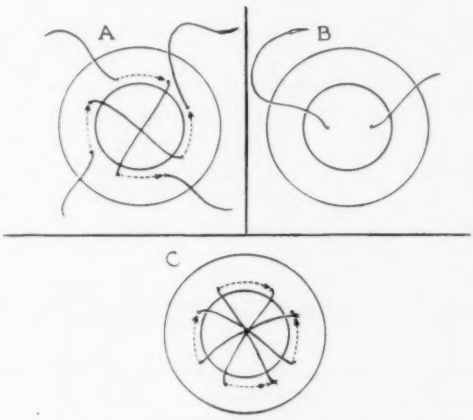


Fig. 2.—New simplified suture for keratoplasty.

3. It is used as a traction suture later, when the dissection of the corneal disk is completed with scissors.

In the matter of corneal sutures, Dr. Gifford and I have been using one which we believe to be simple and yet adequate to maintain the corneal transplant in place (fig. 2).

We have benefited immensely from each of the workers mentioned and have attempted to evolve a technic which is less time consuming, is simplified and is still productive of favorable results.

SOURCES OF TRANSPLANTS

The sources of material for transplantation have been as follows:

1. Eyes of living human beings freshly enucleated because of (*a*) trauma to the globe due to a foreign body or to an accident of any type, irrespective of whether the globe is collapsed, provided the cornea is not injured or macerated; (*b*) severe iridocyclitis without anterior synechias; (*c*) sarcoma, or (*d*) glaucoma.

2. Corneas obtained from stillborn infants.

3. Corneas obtained from infants who have died a few hours or a few days after delivery because of a generalized infection, such as (*a*) pneumonia, (*b*) scarlet fever or (*c*) tuberculosis, or because of an accident, such as a massive hemorrhage of the brain. It is preferable, however, to utilize corneas which have not been involved in any systemic infection.

No difference has been found clinically between the use of corneas from stillborn infants, the use of corneas taken from cadavers [5] and the use of corneas freshly enucleated from living persons, although Filatov and his Russian co-workers claimed that refrigerated corneas yield the best results.

The important considerations are that the corneal epithelium be normal; that there be no edema, blebs or vesicles, and, especially, that the endothelium be normal.

PRESERVATION OF THE CORNEAS

How are the eyes preserved, and what conditions are necessary to maintain their anatomic and physiologic integrity?

The eyes are removed under sterile precautions and placed in a sterile jar, the bottom of which has a layer of sterile cotton saturated with physiologic solution of sodium chloride. The bulb is placed in the jar with the cornea facing upward, care being taken that it does not come in contact with the sides of the jar. The jar is then kept in a specially regulated refrigerator whose temperature varies from 2 to 4 C. Since the corneas absorb oxygen directly from the atmosphere,[6] it might be an added advantage to perfuse oxygen into the sterile jar periodically.

The eyes may be kept under these conditions up to forty-eight hours with a minimal degree of epithelial and endothelial change, although it is preferable to utilize them as early as possible. They are examined under the slit lamp just prior to being used.

4. Castroviejo, R.: (*a*) Keratoplasty, Am. J. Ophth. **15**:825 and 905, 1932; Keratoplasty: Report of Seven Cases, ibid. **17**:932, 1934; (*b*) Queratoplastia, in Concilium internationale ophthalmologicum, 1934, vol. 1, p. 78; (*c*) Keratoplasty, J. M. Soc. New Jersey **32**:80, 1935; (*d*) Queratoplastia: Estudio clínico de catorce casos, Arch. de oftal. hispano-am. **35**:404, 1935; (*e*) Keratoplasty, Tr. Am. Acad. Ophth. **40**:418, 1935; (*f*) Modern Aspects of Corneal Transplantation, read before the Conference on Ophthalmology, American Academy of Ophthalmology and Otolaryngology, 1936; (*g*) Keratoplasty—Microscopic Study of Corneal Grafts, Tr. Am. Ophth. Soc. **35**:355, 1937.

5. Welter, S. L.: An Experimental Study of Suitability of Preserved Cadaveric Corneas for Transplantation Purposes, Kiev, U. S. S. R. Academy of Sciences Press, 1938, p. 48. Fuchs, E.: Zur Keratoplastik, Ztschr. f. Augenh. **5**:1, 1901.

6. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1933, vol. 1, p. 474.

TRANSPLANTATION

Examination of Recipient Eye.—In some cases of leukomatous cornea, the leukoma, although sufficiently dense to cause considerable impairment of vision, allows a good examination of the anterior segment of the eye with the ordinary means of exploration, such as the ophthalmoscope and the slit lamp. Information is thus obtained about the thickness of the cornea, the nature of the opacity and the depth of the anterior chamber; the pupil is studied, and it is determined whether or not anterior or posterior synechias are present. The lens, also, can be examined to some extent if there are transparent areas in the cornea. When the leukoma is very dense, the usual methods of examination do not yield sufficient information and transillumination and infra-red photography are most valuable. Transillumination can be done with an ordinary electric ophthalmoscope provided with a condenser. The transilluminator can be applied to the eyeball behind the region of the ciliary body. The light will pass through the pupil, through a surgical coloboma and through atrophic areas of the iris and ciliary body, revealing something of their shape and position. When the light is turned on and off, the transilluminated pupil may dilate and contract regularly all around. This indicates a free iris. If synechias are present, only part of the pupil will dilate,

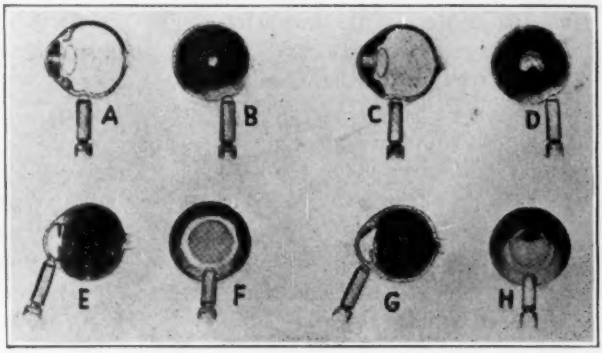


Fig. 3.—Transillumination, reproduced with the permission of R. Castroviejo.

the remainder being immobile. Use of a cycloplegic will provide verification. Absence of a pupillary reaction to light stimulation will indicate that there are large anterior or posterior synechias. The anterior chamber can also be examined by transillumination, according to the method described by Mendoza and Castroviejo [7] for the study of the angle of the anterior chamber, in which the transillumination is applied at the limbus in front of the insertion of the iris. If the anterior chamber is free from synechias, there will be a bright, uniform illumination, not only in the opaque or translucent cornea, but at the limbus in the opaque sclera, corresponding to the region of the angle of the anterior chamber. Anterior synechias will be seen as dark areas, whether peripheral or central, in the illuminated anterior segment.

Indications and Contraindications.—If the patient has no light perception, the operation is performed only for cosmetic purposes. Faulty projection is not always a contraindication.

The operation is definitely contraindicated in cases of glaucoma with or without buphthalmos, even though the tension can be relieved by a preliminary operation.

7. Castroviejo, R.: New Method of Corneal Transplantation, Proc. Staff Meet., Mayo Clin. **6**:417 (July 15); 669 (Nov. 11) 1931.

When there is partial staphyloma or ectatic leukoma, the prognosis is very unfavorable.

Histologic Prerequisites of the Leukoma: The histologic nature of the leukoma, even if all the favorable factors are present, is the most important influence on the fate of the transplanted cornea. Elschnig proved by observation that leukoma is of two types, that in which no corneal elements remain and that in which such elements are present. The prognosis is always better with the second type.

The two types include (1) complete cicatricial leukoma, including leukoma following extensive ulcers of the cornea, for which few successful transplantations have been done, and (2) leukoma containing some transparent corneal lamellas. These may be further subdivided as follows: (*a*) cicatricial leukoma following an ulcer which occupied the whole cornea, with some layers of the corneal elements intact; (*b*) cicatricial leukoma of the central portion of the cornea, with preservation at the periphery of some transparency but not sufficient for a successful optical iridectomy; (*c*) cicatricial superficial leukoma following a burn, trachomatous pannus or herpetic keratitis, and (*d*) leukoma found in the middle and deep layers of the cornea after a parenchymatous keratitis. These four subtypes present the most favorable field for transplantation. Elschnig [8] has conclusively proved that in the case of cicatricial leukoma the transplant must be placed in such a location that its edges come in contact with that part of the cornea which contains the corneal elements even though it may have to be placed eccentrically. This has been clinically demonstrated by our experiences.

Microscopic Studies of the Transplant.—Fuchs, Elschnig, Filatov and Castroviejo have stated the opinion that the transparent corneal graft is a *true* transplant. It retains its individuality and preserves its own cellular elements. According to these authors there is no evidence of a gradual replacement of this type of graft by the tissues of the host, although Salzer [9] disagreed.

For the purpose of classification, cases have been divided into three groups:

1. Those in which conditions are favorable, that is, (*a*) intraocular tension is normal, (*b*) the diseased ocular tissue is limited to the cornea, (*c*) the corneal leukoma is not very dense, although sufficiently so to cause considerable impairment of vision, and (*d*) clear areas surround the leukoma.

2. Those in which conditions are unfavorable, that is, (*a*) a dense leukoma extends over almost the entire cornea, in which case the transplant is surrounded by dense connective tissue in which there is no normal corneal lamellar tissue, (*b*) there is aphakia,[10] (*c*) the intraocular tension is increased or (*d*) there is corneal cloudiness with densely vascularized pannus. In this group of cases preliminary operations must be performed before corneal transplantation in order to prepare a more favorable soil for final keratoplasty. Some of the preliminary operations are to combat glaucoma or to remove synechias. Preliminary iridectomy is performed when the pupil does not dilate fully. The largest vessels supplying a pannus may be destroyed by electrodesiccation, by use of the Denig mucous membrane graft or by beta ray emanations. In cases in which the whole corneal tissue has been destroyed and supplanted by dense scar tissue, it is necessary

8. Elschnig, A.: Keratoplastik, cited by Kuhnt, H., in Elschnig, A.: Augenärzliche Operationslehre, Berlin, Julius Springer, 1922, p. 514. Elschnig, A.: Keratoplasty, Arch. Ophth. **4**:165 (Aug.) 1930.

9. Salzer, F.: Keratoplasty, Ztschr. f. Augenh. **3**:124 and 516, 1900; Beiträge zur keratoplastik, Arch. f. Augenh. **65**:214, 1910; Beiträge zur Keratoplastik: Implantation überlebender Lappen, Arch. f. Ophth. **105**:469, 1921.

10. McArevey, J. B.: Corneal Transplantation in Aphakic Eye, Irish J. M. Sc., October 1937, p. 635.

to perform a series of transplantations, i. e., an amelioration of the leukoma, in order to replace the scar tissue through the cornea with tissue more closely resembling the normal cornea histologically and, finally, to perform a transplantation for visual purposes.

3. Those in which transplantation is done for cosmetic effect alone, i. e., cases in which the eye is amblyopic and there is a dense central leukoma (fig. 4).

The prognosis is favorable in cases of interstitial keratitis in which the Wassermann reaction is negative and the eye "quiet," with a central superficial or deep leukoma and without underlying pathologic change in the iris or synechias; in cases of keratoconus, particularly those in which apical corneal changes are present and the patient is not aided by contact lenses; in cases of injury resulting in blood staining of the cornea, and in cases of central circumscribed corneal leukoma without anterior synechias and with clear peripheral corneal tissue, for example cases of corneal ulcer, serpent ulcer, herpes of the cornea and parenchymatous keratitis.

The prognosis is less favorable in cases of gonorrheal blennorrhea, which may require several preliminary keratoplasties and later one for visual purposes; of tuberculosis of the cornea; of lipoid degeneration of the cornea; of severe lime or acid burns, and of corneal dystrophy.

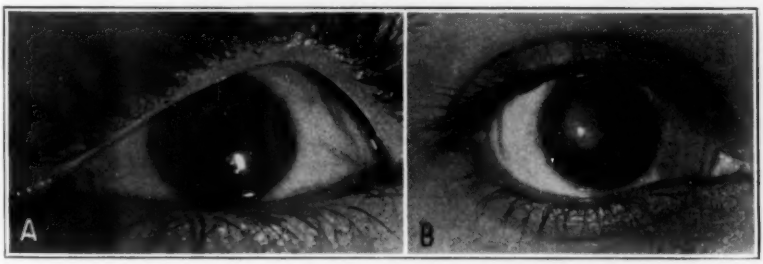


Fig. 4.—*A*, corneal transplant. *B*, corneal leukoma.

REPORT OF CASES

The following brief case histories represent a series of 28 corneal transplantations. These are presented in order to demonstrate specific points of interest.

CASE 1.—C. A., aged 21, had interstitial keratitis in the right eye with old dense corneal vascularization. Vision amounted to light perception and projection in the right eye and was 20/30 in the left. After corneal transplantation was performed on the right eye, the vision was improved to 20/30. However, the corneal graft became opaque three weeks after operation because of a secondary increase in intraocular tension, despite immediate iridectomy.

CASE 2.—H. A., aged 46, had suffered lime burns of both eyes two years before. Vision in the right eye amounted to perception of hand movements, with good projection. That in the left eye amounted to perception of finger movements at 1 foot (30 cm.), with good projection. The left eye showed dense corneal scarring with the vessels growing into the cornea from the superior and inferior portions of the conjunctiva. The right eye showed dense corneal scarring with vessels forming a pseudopterygium nasally and temporally. Corneal transplantation was performed on the right eye by Dr. Gifford, a thirty-six hour cadaver cornea being used (fig. 5). The vision was improved to 5/100. It has been our experience that severe lime burns afford a poor prognosis. This patient, however, was enabled to see colors, to dress himself and to get around without assistance.

CASE 3.—A boy aged 16 had bilateral interstitial keratitis. After intensive antisyphilitic treatment of nine months' duration, vision was 20/200 in the right eye and in the left it amounted to light perception and projection and color perception. On June 21, 1941 corneal transplantation, with avertin anesthesia, was performed on the left eye (fig. 6). The donor

cornea was obtained from a freshly enucleated injured eye. A 5.5 mm. circular corneal disk was used. The patient was given cevitamic acid and riboflavin during his two week hospitalization. Three months after the corneal transplantation the vision in the left eye was 20/20 and Jaeger type 1 could be read at 14 inches (35 cm.). No glasses were necessary. Homatropine refraction revealed an error of + 0.25 D. sph. ⌒ + 0.50 D. cyl., axis 15. On March 14, 1942, vision in the left eye was unchanged, and the transplant was uniformly clear.

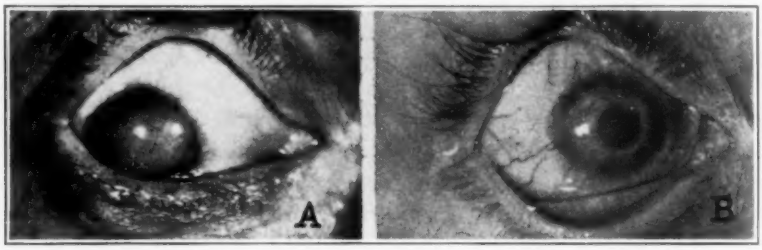


Fig. 5 (case 2).—*A*, before operation. *B*, after operation.

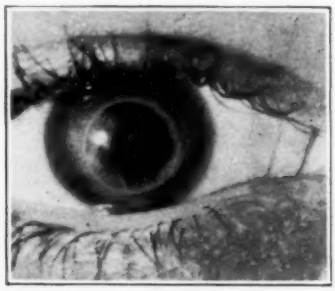


Fig. 6 (case 3).—Corneal transplant.

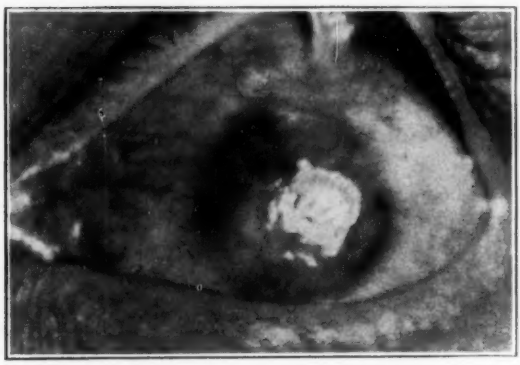


Fig. 7 (case 5).—Lime burn of cornea.

The patient continued to receive antisyphilitic treatment and riboflavin, especially since recent research has demonstrated that riboflavin has a beneficial effect on the oxidation of corneal tissue. The boy is now employed gainfully in a defense plant.

Case 4.—A woman aged 22 was found to have an adherent leukoma in the right eye as a result of measles in infancy. Vision amounted to light perception and projection in the right eye and was 20/30 in the left. Corneal transplantation was performed on the right eye for cosmetic purposes only. The donor cornea was from a stillborn infant. The result was a clear, transparent cornea.

Comment.—The cornea remained clear for six months, until the patient went swimming; immediately afterward she noticed that it was completely opaque again.

CASE 5.—A. H. had an old severe penetrating lime burn of the left cornea with superficial and deep vascularization. Vision in the right eye was 20/30 and in the left amounted to light perception and projection. The patient had had intensive roentgen ray therapy (a series of twelve treatments) to the cornea, consisting of one third of an erythema dose. After three months, corneal transplantation was done on the left eye. The donor cornea was obtained from a stillborn infant. The patient was given roentgen ray therapy to the cornea two hours after operation and on the first, second and third postoperative days. The corneal graft remained clear for three weeks, during which time the vision was improved to 20/100. Gradually the graft became translucent, and the corneal vascularization recurred.

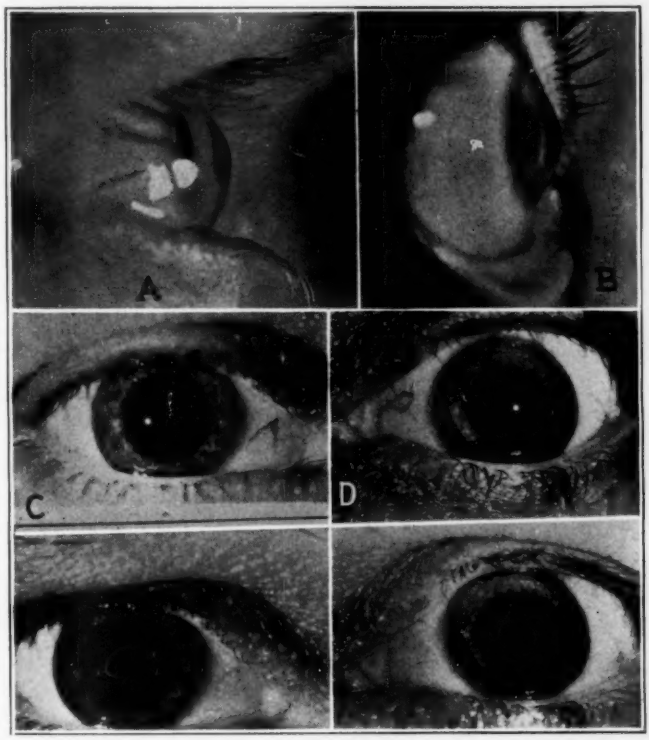


Fig. 8 (case 6).—*A*, keratoconus before operation. *B*, after operation, demonstrating the flattened corneal apex. *C*, asymmetric corneal mires before corneal transplantation. *D*, symmetric corneal mires after corneal transplantation.

Comment.—Roentgen ray therapy for corneal vascularization was used in this case in an effort to substantiate some of the claims made for it.

CASE 6.—A. J., a woman aged 32, was found to have bilateral far advanced keratoconus. Vision was 6/200 in the right and 3/200 in the left eye; no Jaeger type could be read. No improvement could be obtained with cylindric correction for high myopia. The patient was consequently fitted with contact lenses, but because of the extreme apex of the corneal cone she could not tolerate them. Slit lamp examination revealed early scarring of the apex. On Nov. 26, 1939 keratoplasty was performed on the left eye, a twenty-four hour, 4.5 mm. corneal disk from a stillborn infant being used. The corneal graft was completely clear and the line of demarcation between the transplant and the cornea barely visible. The patient at the

time of writing was wearing a contact lens comfortably for periods of seven hours. She now enjoys the pleasure of movies, which she was previously denied. The vision in the left eye was 20/40, and Jaeger type 1 could be read at 13 inches.

Comment.—With keratoconus the prognosis is most favorable. A small corneal graft is preferable.

CASE 7.—The patient had bilateral Groenouw's dystrophy. Vision was 10/200 in the right eye and amounted to light perception and projection in the left. A keratoplasty was performed on the left eye. The donor cornea was obtained from a stillborn Negro infant. The graft was slightly edematous and gray on the first postoperative day and clear on the second. On the third day it became crystal clear, and it remained so on the fourth day. On the fifth and sixth postoperative days it was slightly edematous. On the seventh day it was slightly gray. It was more dull on the eighth day, opalescent on the ninth and translucent on the tenth. On the eleventh day it became opaque.

Comment.—In my opinion this case presents clinical evidence of an abnormal tissue reaction. The graft was crystal clear for five days and then rapidly became opaque. There was no technical error, and the anterior chamber was reformed early, on the third postoperative day.

Fig. 9 (case 8).—Result of corneal graft.

CASE 8.—J. R., aged 33 years, stated that both eyes had been burned in June 1938 as a result of an explosion. There was moderate loss of substance in the center of the right cornea, and many fine particles of a nonmetallic substance were present in the cornea and conjunctiva. On August 2 vision in the right amounted to light perception and projection; there was a cicatricial ectropion with marked loss of skin under the lid. A plastic operation was performed on the right lid. On October 31 an optical iridectomy was performed. On July 16, 1939 a keratoplasty was performed on the right eye by Dr. Gifford. Vision in the right eye on June 15, 1942 was 20/200, correctable to 20/70 with a + 6.00 D. sphere and to 20/50 with a contact lens.

Comment.—It was necessary in this case to perform an iridectomy in order to remove the anterior synechia before doing the corneal transplant.

CASE 9.—J. T. was injured in an explosion on Jan. 2, 1938. At examination the right cornea was full of fine particles in the superficial layers. The left eye had to be enucleated because of complete corneal sloughing. On December 8 a superficial keratectomy was performed on the right eye, after which the vision improved to 3/200. On Feb. 13, 1939 an iridectomy at 2 o'clock was done. This was followed on April 15, 1940 by a corneal transplantation on the right eye by Dr. Gifford. On May 1, 1942 vision in the right eye with a correction of — 1.50 D. sph. ⌣ — 1.50 D. cyl., axis 50 was 20/50. A prosthesis was worn in the left eye.

Comment.—The cornea in this case was prepared by a preliminary iridectomy and superficial keratectomy before corneal transplantation was performed.

CASE 10.—G. W. had bilateral old interstitial keratitis. Vision amounted to light perception and projection in the right eye and to light perception alone in the left. The donor eye was enucleated because of chronic iridocyclitis. Slit lamp examination revealed no anterior synechias, and the epithelium was normal. A 5.5 mm. disk was removed.

Comment.—Both corneas had a bluish ground glass appearance, and both were completely opaque over the entire surface. Preliminary examination was unsatisfactory even with transillumination. The prognosis was admittedly unfavorable because of extensive and complete leukoma. However, after corneal transplan-

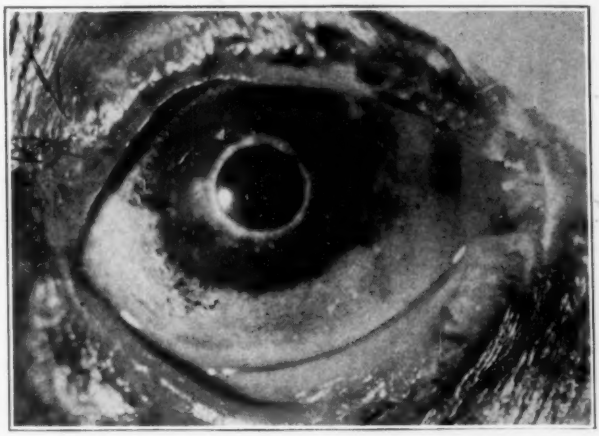


Fig. 10 (case 9).—Corneal transplant.

Fig. 11 (case 10).—Old interstitial keratitis with complete leukoma of both corneas.

tation it was noticed that the cornea surrounding the graft became less and less opaque for three weeks and then gradually returned to its original state.

CASE 11.—G. Z., a girl aged 17, had old interstitial keratitis in the left eye with a central corneal leukoma, which had followed perforating ulcer, and left divergent strabismus. On April 24, 1929 a muscle operation was done to produce parallelism. Vision was 20/65 in the right eye and amounted to perception of hand movements at 1 foot (30 cm.) in the left. On Aug. 4, 1938 an optical iridectomy was performed for the removal of anterior synechias. On November 8 a keratoplasty was done for cosmetic purposes. On March 11, 1939 vision was 20/200 in the left eye, with the cornea completely clear throughout.

Comments.—The patient was definitely in need of rehabilitation from a cosmetic standpoint. The divergent strabismus was corrected, then a preliminary iridectomy was done to remove the anterior synechias and later a corneal transplantation was performed to remove the hideous and very apparent scar.

CONCLUSION

The technics of outstanding contributors in this field have been clinically appraised and evaluated. I have found a simplified technic to be less time consuming and to be productive of favorable results. By use of unselected clinical material, I have been able to arrive at a clinical evaluation of eyes presenting a favorable or an unfavorable prognosis with regard to corneal transplantation, and to reach some conclusions as to the commonest causes of failure.

30 North Michigan Avenue.

BILATERAL METASTATIC CARCINOMA OF THE CHOROID

ARTHUR J. BEDELL, M.D.
ALBANY, N. Y.

Metastatic carcinoma of the choroid is a comparatively rare condition. It was first presented in a pathologic report in 1872 by Perls.[1] Since that time approximately 250 cases have been published or reported in discussions.

The literature has been completely reviewed by Marshall,[2] Krukenberg,[3] Parsons,[4] Oatman,[5] Suker and Grosvenor,[6] Ask,[7] Lemoine and McLeod[8] and others.[9] Many of the reports are only summaries of the pathologic examination, for comparatively few eyes have been examined before the detachment of the retina.

Among cases in which the fundus was described are 2 reported by de Schweinitz[10] in 1898. In one there was a broad, flat, grayish yellow elevation, the

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3. Krukenberg, F.: Zur Lehre vom metastatischen Carcinom der Chorioidea, Klin. Monatsbl. f. Augenh. **41**:145, 1903.

4. Parsons, J. H.: Diffuse Sarcomata of the Uveal Tract, Arch. Ophth. **33**:101, 1904.

5. Oatman, E. L.: Metastatic Carcinoma of the Choroid, Am. J. M. Sc. **151**:375, 1903; Diagnostics of the Fundus Oculi, Troy, N. Y., Southworth Co., 1913, p. 277.

6. Suker, G., and Grosvenor, L. N.: Metastatic Carcinoma of the Chorioid, Tr. Am. Acad. Ophth. **13**:148, 1908; Ophthalmology **5**:580, 1908.

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10. de Schweinitz, G. E.: Two Cases of Metastatic Carcinoma of the Choroid, Tr. Am. Ophth. Soc. **8**:313, 1898.

summit of which was best seen with a + 6.00 D. sph. lens. This gradually merged, without a distinct line of separation, into the surrounding choroid, beginning near the edge of the optic disk, covering the macula and extending some distance beyond it. In de Schweinitz' other case the margins of the disk were blurred. The macular region was occupied by a somewhat irregular growth. The summit was best seen with a + 4.00 D. sph. lens. It was grayish and dotted here and there with reddish spots. This elevation shaded gradually into the surrounding choroid without a sharp line of demarcation, extending downward as far as it could be traced but upward less markedly.

Jack's [11] case was not observed until the retina was separated in the right eye; later it became detached in the left. It is important, however, because Verhoeff [12] made the pathologic examination, found two flattened tumor nodules and stated that the growth was metastatic because it spread over the fundus.

Reese [13] stated that of his collection of 22 eyes with carcinoma, in all but 3 there was complete detachment of the retina.

Morgan [14] noted a central detachment of the retina, which appeared solid. In DeLong's [9a] case, the fundus examination was not satisfactory. The growth in the choroid was carcinoma.

In A. Knapp's [15] case, observed eight years after removal of the left breast, the ciliary body was involved by a grayish white tumor covered with a curious flaky white material.

Cohen's [16] experience was unusual, for both eyes in his case suddenly became defective and the tumor was practically identical in the two: flat, sharply circumscribed, grayish and moderately pigmented.

In Hirschberg's [17] case, in the right eye there was a yellowish pink tumor 2 mm. high around the nervehead and in the left eye a tumor 1 mm. high.

Schöler [18] reported a detachment in the right eye with a gray ring about the disk, while in the left there were pinhead dots about the macula and deposits on the disk and retina.

Stock [19] said the growth looked like round cell sarcoma.

Weeks [20] had 2 cases. In one a detachment of the retina measured 2.7 mm., with the retina normal in the periphery. In the other there was a brown mass beneath the detached retina.

Holden and Rusk [21] saw a complete detachment of the left retina secondary to ovarian carcinoma.

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11. Jack, E. E.: A Case of Double Metastatic Carcinoma, Tr. Am. Ophth. Soc. **9**:483, 1902.
12. Verhoeff, F. H.: Pathological Report on Dr. Jack's Case of Metastatic Carcinoma of the Choroid, Tr. Am. Ophth. Soc. **9**:485, 1902.
13. Reese, A. B., in discussion on Lemoine and McLeod.[8a]
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15. Knapp, A.: Metastatic Carcinoma of the Ciliary Body, Arch. Ophth. **1**:604 (May) 1929.
16. Cohen, M.: Bilateral Metastatic Carcinoma of the Choroid, Arch. Ophth. **54**:205, 1925.
17. Hirschberg, J.: Einen Fall von doppelseitiger metastatischer Aderhautcarcinose, Centralbl. f. prakt. Augenh. **6**:376, 1882.
18. Schöler: Fall einer Erblindung in Folge doppelseitigen metastatischen Aderhaut-Carcinoms, Centralbl. f. prakt. Augenh. **7**:236, 1883.
19. Stock, W.: Ein doppelseitiges metastatisches Hypernephrom der Uvea, Klin. Monatsbl. f. Augenh. **78**:116, 1927.
20. Weeks, J.: Report of Two Cases of Metastatic Carcinoma of the Choroid and One Case of Myxosarcoma of the Orbit, Tr. Am. Ophth. Soc. **14**:326, 1915.
21. Holden, W. A., and Rusk, G. Y.: Metastatic Carcinoma of the Choroid from a Primary Growth in the Ovary, Arch. Ophth. **33**:322, 1904.

Dickson and Benedict [22] noted edema of the disk and detachment of the retina in the lower nasal quadrant, with considerable choroidal disturbance, secondary to rectal carcinoma.

Jensen [23] reported a flat, grayish elevation in the retina of the right eye just temporal to and involving the macular area. It was about 2.5 disk diameters in width and about 2 D. in elevation. There was slight pigmentation over the area. The retina was smooth and the vessels regular in course. There was a small area of pigmentation in the opposite eye, below and temporal to the disk. Three months later the growth was much larger, with an elevation of 6 D. in the right eye and 8 D. in the left. Later there was a smooth, gray detachment of the retina.

Kulvin [24] referred to a "disk edema"; the retina was detached below the disk and laterally, with small knoblike dilatations of the end vessels on a pigmented mass elevated 6 D.

Lemoine and McLeod's [8] patient was first seen with a detachment in the lower half of the left retina; later there was involvement of the right eye, with several hemorrhages in the deeper layers of the retina.

Usher [25] described the appearance in one of his cases in which in the left eye above and immediately external to the fovea there was a great swelling with an ill defined margin occupying an area about the size of two optic disks. There were no hemorrhages, and the elevation was 6 D. Later there was a detachment of the retina. In his second case there was a diffuse gray swelling immediately below the left optic disk and macula. Later this extended to the upper part of the macula. The retinal vessels were not tortuous. The elevation was 6 D.

Luzsa [26] referred to a foamy mass in the right eye 6 disk diameters supernasally from the disk, which was sharply outlined and elevated. Subsequently an oval pale area appeared about the fovea. The course of the artery seemed to be interrupted at various points. In the left, the opposite, eye, there was a kidney-shaped, elevated, sharp-margined, pigmented area surrounded by hemorrhages and two grayish detachments. He spoke of anemic-like areas which he thought were due to emboli.

Oatman [5] described the typical appearance as a flat oval deposit, "dirty yellow with pigment spots" and a center elevation of 1 to 2 mm., gradually sloping into the surrounding fundus.

Ask [7] referred to the upper half of the macula, which was a yellow-red oval 2 by 3 disk diameters raised 2 D. Three days after he first saw the patient there was a 5 to 6 D. swelling. When Ask finished his report he detailed 211 cases and stated that of 152 the proved pathologic source of metastasis was the breast in 76, lung in 20, esophagus in 2, ventricle in 5, rectum in 2, pancreas in 1, liver in 2, prostate in 5, kidney in 3, thyroid in 3, adrenal in 1, parotid in 1 and thymus in 1. In 2 cases the metastasis arose from chorioepithelioma and in 2 from malignant melanoma, and in 25 the source was unknown.

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22. Dickson, C. F., and Benedict, W. L.: Adeno-Carcinoma of the Sigmoid with Metastasis of the Eye, Am. J. Surg. **15**:99, 1932.

23. Jensen, A. F.: Bilateral Metastasis to Eye Following Carcinoma of the Breast, Am. J. Ophth. **63**:24, 1941.

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25. Usher, C. H.: Cases of Metastatic Carcinoma of the Choroid and Iris, Brit. J. Ophth. **7**:10, 1923; Frequency of Metastatic Carcinoma of the Choroid, ibid. **10**:180, 1926.

26. Luzsa, A.: Brustdrüsenkrebsmetastase in beiden Augen, Klin. Monatsbl. f. Augenh. **105**:495, 1940.

Clapp [27] in a discussion of the Lemoine and McLeod paper, reported 3 cases. In one there was a yellowish elevated mass at the temporal side of the nerve; in the second, diffuse elevated areas throughout the fundi, and in the third, a grayish elevated mass in the fundus of the right eye. In his 2 cases reported in 1926 the patient had detachment of the retina when first seen.

In the McDannald and Payne [28] case the fundus was normal to within about 2 disk diameters of the optic nerve on the temporal side. A light gray slightly elevated mass extended into the disk. There were no hemorrhages or exudates, and no pigment on the oval mass. The enucleated eye showed the growth in the nerve, the retina and the choroid.

Metastatic carcinoma of the optic nerve was described by Davis [9f] in 1932. The 8 by 10 D. swelling to the temporal side of the retina was grayish white, with small dark dots and larger pigmented areas.

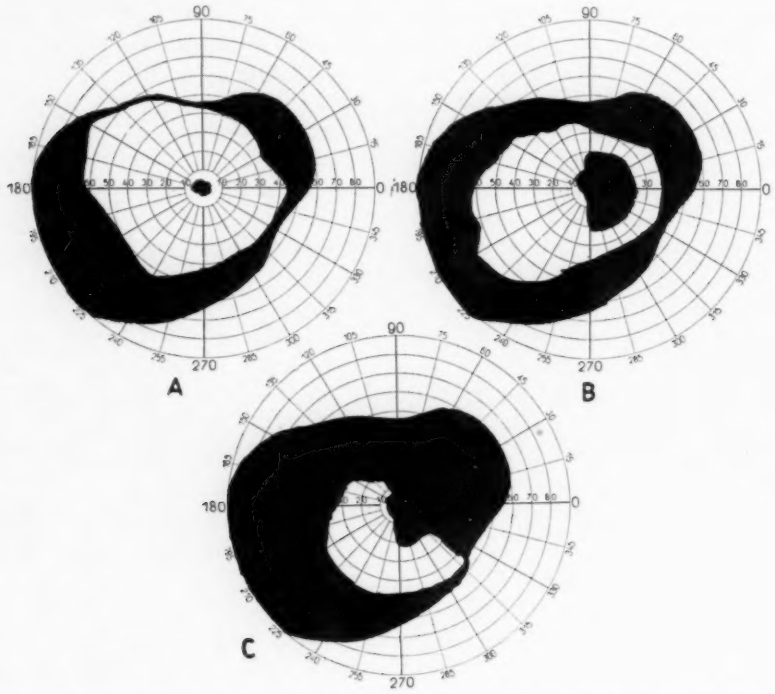

Fig. 1.—The visual field of the right eye Aug. 27, 1938 (*A*), Nov. 3, 1938 (*B*) and April 5, 1939 (*C*). A 1/330 mm. test object was used.

LaGrange [29] simply stated that the growth was secondary involvement of the choroid.

Suker and Grosvenor [6] said that the retina was attached to the underlying tumor.

Greenwood [30] reported 4 cases. In the first there was a retinal detachment over a flat grayish white mass, metastasis being from the prostate. In the second, a flat

27. Clapp, C. A.: Metastatic Carcinoma of the Choroid with Report of Two Cases: Four Eyes, Am. J. Ophth. **9**:513, 1926.

28. McDannald, C. E., and Payne, B. F.: Metastatic Carcinoma of the Optic Nerve and Choroid, Arch. Ophth. **12**:86 (July) 1934.

29. LaGrange, M.: Carcinome metastatique de la choroide, Ann. d'ocul. **119**:56, 1898.

30. Greenwood, A.: Carcinoma of the Choroid, Tr. Internat. Cong. Ophth. **1**:567, 1922; Am. J. Ophth. **5**:912, 1922.

Fig. 2.—Fundus of the right eye Aug. 9, 1938.

Fig. 3.—Fundus of the left eye Aug. 9, 1938.

white mass of cheeselike substance was present beneath the detached retina. Four months later there appeared in the other eye a whitish flat mass 2 disk diameters up and out from the disk. Metastasis was from the breast. In the third case, in the right eye a white discoid tumor was seen through a detachment and in the left eye a grayish white mass. Metastasis was from the breast. In the fourth case the right eye presented a flat discoid subretinal mass down and out from the macula, 3 disk diameters in extent. The center was whiter than the periphery. Metastasis in this case also was from the breast.

Moore and Stallard [31] together observed 6 cases. In some there were knobby growths in the choroid, secondary to pulmonary involvement.

In the case here reported not only are the pathologic observations described but the clinical history from the onset to detachment of the retina and secondary glaucoma is stressed.

L. C., a woman aged 49, was first seen Aug. 9, 1938, at which time she said that for the past several months the sight of the right eye had been failing. Close questioning revealed that in September 1934 the right breast and axillary glands were removed by radical excision and that roentgen ray treatments were subsequently given.

Her physician, Dr. Catherine A. Welsh, reported that there were several carious teeth. The chest showed a large right mastectomy scar extending into the axilla. The left breast was normal. No abnormal signs were elicited in either lung. The heart was normal except for a slightly accentuated aortic second sound. Blood pressure readings on different occasions were 180 systolic and 110 diastolic, 150 and 100 and 150 and 100. Neurologic examination revealed that the pupils were equal and regular and reacted to light and in accommodation. There was slow nystagmus on lateral gaze to the right; the biceps, triceps, knee, ankle and abdominal reflexes were equal and active; sensation and motor power were normal; no abnormal reflexes were elicited. There were no enlarged lymph nodes.

The urine was normal. The blood count was within normal limits. The Wassermann and Kline reactions of the blood were negative. A roentgenogram of the chest showed a small calcified focus in the right upper lobe but was otherwise normal. A teleroentgenogram showed the measurement of the heart to be within normal limits and that of the aorta to be slightly greater than normal. An electrocardiogram showed left deviation of the electrical axis, regular sinus rhythm and normal PR intervals and QRS complexes. Roentgenograms of the sinuses showed no abnormality.

After a complete series of roentgenograms of the teeth had been taken, six carious teeth were removed, on four of which were apical abscesses.

On August 9, vision in the right eye was 6/30 with ability to read Jaeger type 19. The globe was freely movable and externally normal. The pupil measured 3 mm. and was regular and active. The media were clear. The disk was clearly outlined and the retinal vessels normal. Starting about 1¼ disk diameters from the temporal side of the disk and extending about 4 disk diameters outward was a pale, yellowish pink, obliquely oval area measuring about 3½ disk diameters across and about 1 D. in elevation. The edge nearest the disk was irregular and fairly well distinguished from the adjacent normal retina, which was a darker color. The rest of the border was flat and merged into the retina. The surface of the tumor was almost smooth, with scattered flecks of brownish pigment just beneath it. The central portion was the least pigmented. The retinal vessels passed over the slightly elevated lesion without kinks or angulations. There was an irregular central scotoma at about 7 by 5 by 120 degrees, and the field was concentrically contracted about 15 degrees.

The vision of the left eye was 6/6 with ability to read Jaeger type 12. Externally the eye was normal, and it was freely movable. The pupil measured 3 mm. and was regular and active. The media were clear. The disk was clearly outlined, and the retinal vessels were normal. Extending from about ½ disk diameter beyond the superior temporal edge of the disk was a flat, smooth, horizontally oval pale yellow-gray mass measuring 2 by 2½ disk diameters; it had well defined borders almost devoid of pigment except on the lower and outer edges, which were brownish gray. Below this area was a much thinner indefinite, yellow-pink extension best defined between the major branches of the superior retinal vessels shortly after they crossed the upper edge of the disk. The vessels passed over the lesion without change in course, level or caliber. The remaining portions of the fundus were normal. The field of vision was not contracted, although there was a partial scotoma in the inferior nasal quadrant.

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31. Moore, R. F., and Stallard, H. B.: Metastatic Carcinoma of the Choroid: A Report of Two Cases Where the Primary Neoplasm Was in the Lungs, Brit. J. Ophth. **16**:532, 1932.

Nineteen days later, on August 27, the only noteworthy change was in the center of the tumor, where a pale oval about 1¼ disk diameter was raised 2 D. above the surrounding level. There were fewer pigment flecks in it, but the temporal edge was a narrow brown line. Some weeks later, on November 3, the scotoma was much larger, extending into the nasal field 22 degrees from the point of fixation. The peripheral field was more contracted. The changes in the visual field were readily explained by the alterations in the lesion. The pigmented flakes were larger, and the disk side of the tumor was more easily seen. In the temporal part of the area there was a cloudy, yellow swelling about 1.5 D. high. The differences in level were determined by tracing the retinal vessels. The superior branches were flat, but an inferior one, extending over the edematous part of the growth, was elevated and showed a decreased vessel wall reflex, greatest to the temporal side. Above the translucent swelling was a less definite mass, which partially concealed some of the finer vessels and looked like a white fluffy exudate.

In the left eye the tumor had expanded downward until it was in contact with the disk and encircled the upper-outer two fifths of its margin, increasing the paler pink area so that the involved region was 2½ disk diameters.

Dr. Arnold Knapp saw the patient in consultation December 13 and advised against enucleation at that time because the patient was comfortable and the growth metastatic.

On December 15 the central and outer portions of the tumor were paler than they had been six weeks before. Both the upper and the lower terminal vessels were obscured, and a collection of dense brown pigment was present near the center, suggesting an umbilication with a rounded periphery. The tumor, which had expanded temporally about 2 disk diameters, was still smooth.

On Jan. 19, 1939 examination disclosed that since the previous visit the vision had failed until it was only 1/200 eccentrically. The field of vision was a small inferior temporal quadrant. The tumor had expanded in all directions. Above it reached a major vessel; toward the disk it was 1 disk diameter wider and temporally about 3 disk diameters. The entire mass was paler because the pigment was decreased. The outer portion was whiter, less transparent and more elevated. The central pigmentation was on a deeper level than before.

Three months later, on April 5, the tumor had further increased, covering about twice as much surface as when first seen. With the enlargement there was a reduction in the color until it was almost the shade of the disk, and the pigmented specks were less conspicuous, being partially obscured by the overlying opaque tumor, so that they appeared as fine brownish grains. The region of central pallor was a thick white raised mount through which the pigmented spot was faintly visible. On the disk side there were several isolated pigmentations arranged as curved lines veiling the underlying vessels. There were also several minute hemorrhages. There had been a striking change in the retinal vessels, which were now attenuated, with marked variations in the lumens. Until this time there had been no perceptible extension in the left eye. Now, however, the tumor was almost three times as large as when first seen. The expansion had been rather uniform, with an increase in the number and density of the flecks of pigment. In color, general appearance and consistency the tumor was similar to that first noted in the right eye. The vision was 6/7.5.

As the growth enlarged it grew a little thicker and thus seemed to cover and obscure the pigment flakes as well as to spread them farther and farther apart, except in some special collections, such as that near the center of the tumor in the right eye. This process was of considerable value as a definite sign of a progressing tumor.

On August 1 a cloud came before the right eye, and soon thereafter the sight was lost. The vision amounted to faint perception of light, the pupil measured 4 mm. and the retina was completely detached. The ocular tension was normal.

In the left eye the tumor in the superior quadrant was larger, showing not only the pale area noted but a thinner, pinker lower portion. The vision was unimpaired.

On October 3 the right eyeball was congested and the cornea steamy. The pupils measured 4.5 mm. and the fundus could not be seen. Ocular tension with the new Schiøtz tonometer was 57. Enucleation was advised because of the glaucoma and excruciating pain. The right globe was removed the next day.

On October 12 there were several superficial granular hemorrhages in the left eye arranged in two distinct groups. One extended 1 disk diameter upward from the upper nasal edge of the disk, with a curved lower end and a vertical shaft. The other, oblique about axis 30 degrees, spread from the disk margin for 1 disk diameter.

The hemorrhages had disappeared by November 19, and, although the tumor was larger and more mottled, the changes were not proximate to the fresh blood.

When the patient was last seen, on April 10, 1940, the right socket was free from any evidence of metastasis. The vision of the left eye was 6/15. There had been no increase in the size of the superior tumor mass, but the pigment was in flecks similar to those observed in the right eye eighteen months previously. Below and to the temporal side was a new, large, flat mass elevated only about 1.5 D. It was a pale pink tumor more than 3 disk diameters in size with a few scattered brownish pigmentations. The retinal vessels were unchanged and

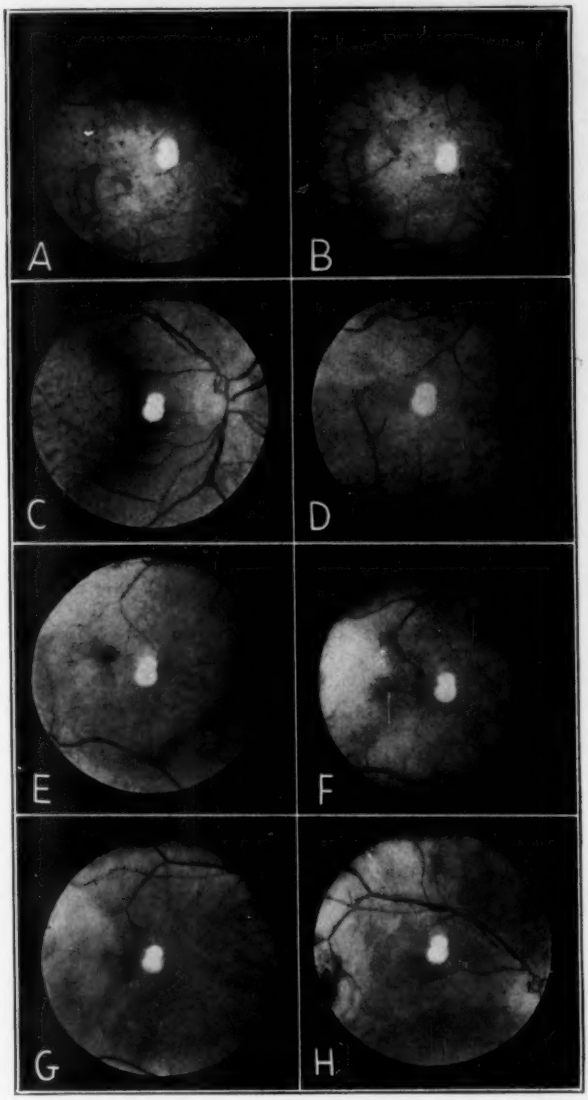

Fig. 4.—Development of carcinoma of the choroid in the right eye: *A* and *B*, Aug. 27, 1938; *C* and *D*, Nov. 3, 1938; *E*, Dec. 15, 1938; *F*, Jan. 19, 1939; *G* and *H*, April 5, 1939.

continued their course without interruption or deflection. There was a 10 degree oval central scotoma, with marked peripheral contraction and slight enlargement of the blindspot. The patient was in excellent spirits, followed her usual routine and was without pain.

On October 19, while sitting up, she had a convulsion which lasted fifteen minutes and from which she did not entirely recover for an hour. The following day she had four convulsions and passed into a deep coma; she died November 26.

Dr. Ellis Kellert sent the following report concerning the primary tumor of the breast:

"The tumor of the mammary gland was in the form of numerous nests of cells lying apparently in tissue spaces. The cell clusters varied greatly in size but in general were anaplastic; the cells were large and contained prominent, pale-staining nuclei of fairly uniform size; an occasional mitotic figure was present. Mingled with these clusters were many cell groups having distinct acini and still others in which attempted acinus formation was evident.

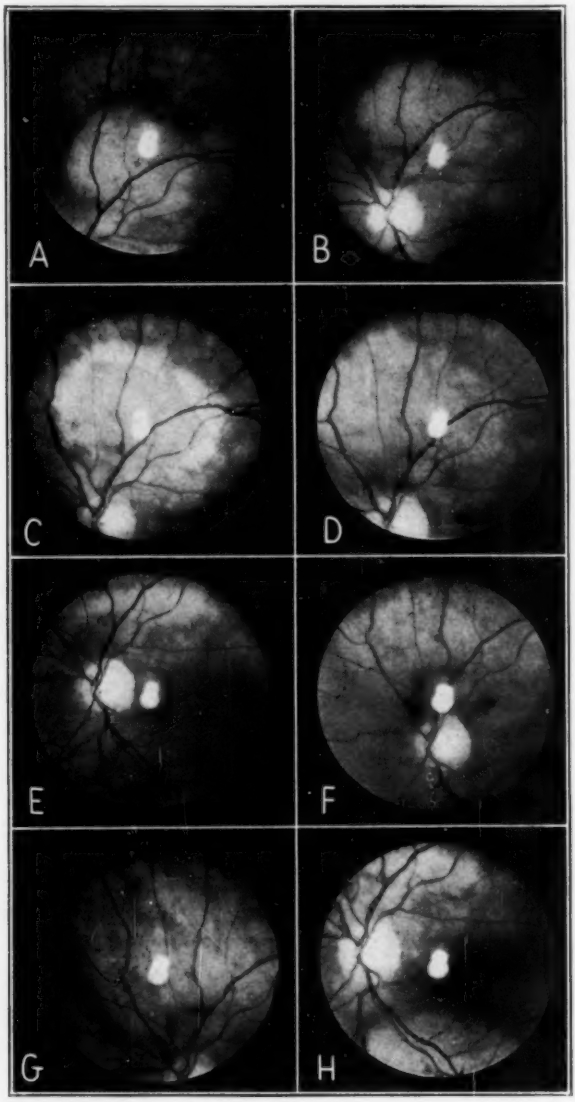

Fig. 5.—Development of carcinoma of the choroid in the left eye: *A*, Aug. 9, 1938; *B*, Nov. 3, 1938; *C*, April 5, 1939; *D* and *E*, Aug. 23, 1939; *F*, Oct. 12, 1939; *G*, Nov. 19, 1939; *H*, April 10, 1940.

An occasional ductlike structure appeared, distended with necrotic cellular elements and debris and lined by thick layers of tumor epithelium containing distinct acini and small cystic areas. The dense fibrous stroma was abundant and liberally sprinkled with lymphocytes. Sections of lymph nodes showed almost complete replacement by tumor similar to that in the breast. There was, however, much less adeno arrangement and no increase in mitoses. The lymphatic channels in the capsules of the nodes were crowded with tumor cells."

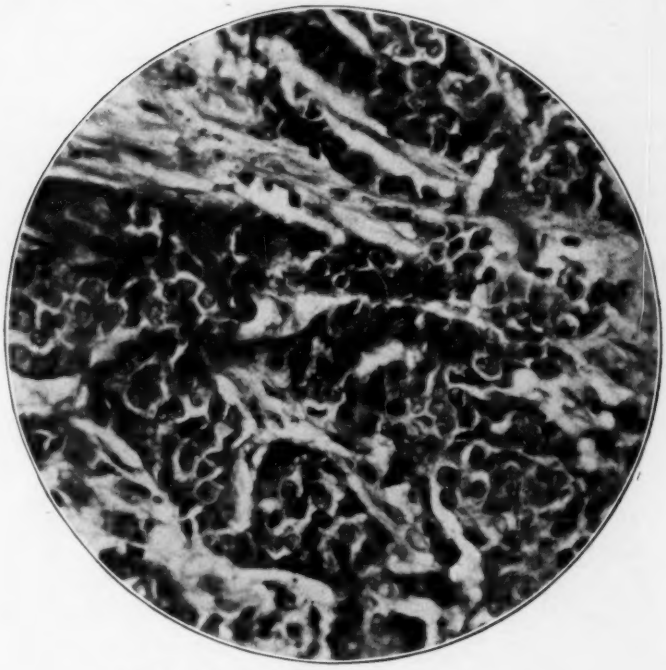

Fig. 6.—The tumor of the breast (× 335).

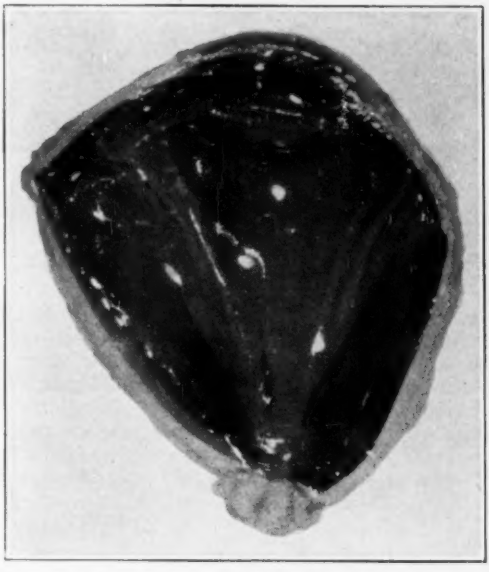

Fig. 7.—Gross section of the right eyeball. The gray choroidal tumor extends from the optic nerve forward on the temporal side, left in the picture, to the ciliary body.

On section of the right eyeball the anterior chamber was seen to be shallow, the lens pushed forward and the retina completely detached, a large pale encircling mass occupied the temporal half of the choroid. In places this was about 2.5 mm. thick.

Dr. John J. Clemmer, director of the Bender Laboratory, reported adenocarcinoma, metastatic to the choroid.

Dr. Theodore L. Terry also examined the specimen, and a digest of his report follows:

"The pathologic diagnosis was metastatic carcinoma of the choroid. There were separation of the retina, colloidal excrescences and secondary glaucoma.

Microscopically, there was slight cystoid degeneration near the ora serrata. The retinal ganglion cells appeared reduced in number. The choroid was largely replaced by carcinoma. Most of the choroidal blood vessels had disappeared. Various amounts of choroidal stroma containing pigment could still be identified. No newly formed blood vessels were observed. There was, however, some newly formed connective tissue acting as a stroma for the neoplasm. The cells of the neoplasm itself were of ectodermal type. Few mitotic figures were observed. In fact, the tumor appeared to be growing very slowly. In spite of the few blood vessels observed,

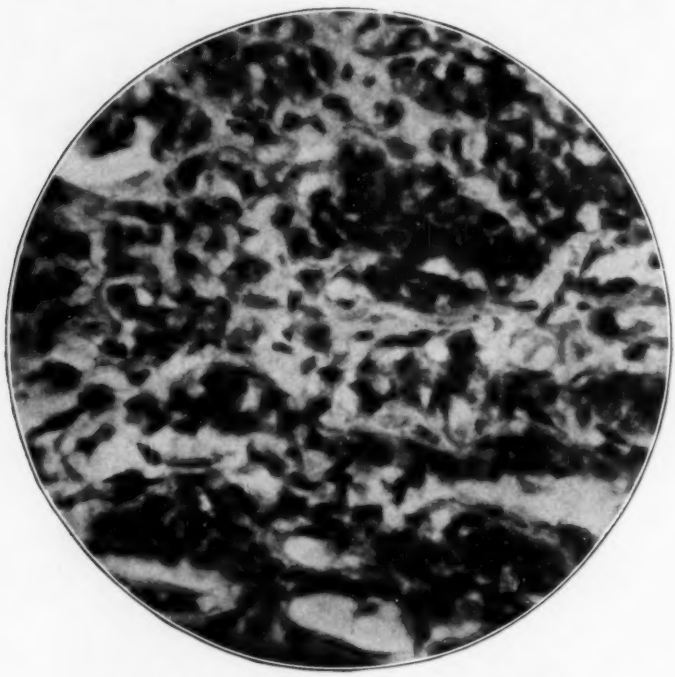

Fig. 8.—The choroidal tumor, right eye (× 335).

necrosis was extremely slight. The ectodermal cells making up the neoplasm were arranged for the most part in glandlike structure. The lumens of the glands invariably appeared empty. The neoplasm should be diagnosed as adenocarcinoma of low grade malignancy originating from gland-forming tissue. Although the tumor extended throughout the choroid and the suprachoroidea, its involvement of the sclera was almost nil. In several places the pigment epithelium of the retina had proliferated and a few nodules had formed, which in time perhaps would have given rise to colloidal excrescences. This tumor might have been relatively flat because of its low grade invasive growth, which would tend to spread it out over the extent of the choroid."

Usher [25] in a review of 110 cases found that the average duration of life after the ocular lesion had been noted was eight months, the longest two years and the shortest four weeks. The great majority of patients were cachectic, with multiple metastases.

The duration of life after the discovery of the choroidal tumor depends on so many variable factors that the conclusions are of comparatively little value. If

a patient is first examined when in the terminal stage of cancer, surely the life expectancy will be shorter than if the tumor of the eye is small and the patient in a comparatively good general condition.

It would seem from the published descriptions by Marshall, Oatman and others and from the observations in the case here reported that the characteristic fundus change is primarily the appearance of a flat, pale, pink-gray area with a delimiting border which is faintly pigmented and with the extension in surface rather than in thickness. The tumor is usually thin. After a time there is a detachment of the retina with or without subsequent glaucoma. In most cases the growth eventually becomes bilateral, although the tumor is usually much more advanced in one than in the other eye. The location of choice is the perimacula, but

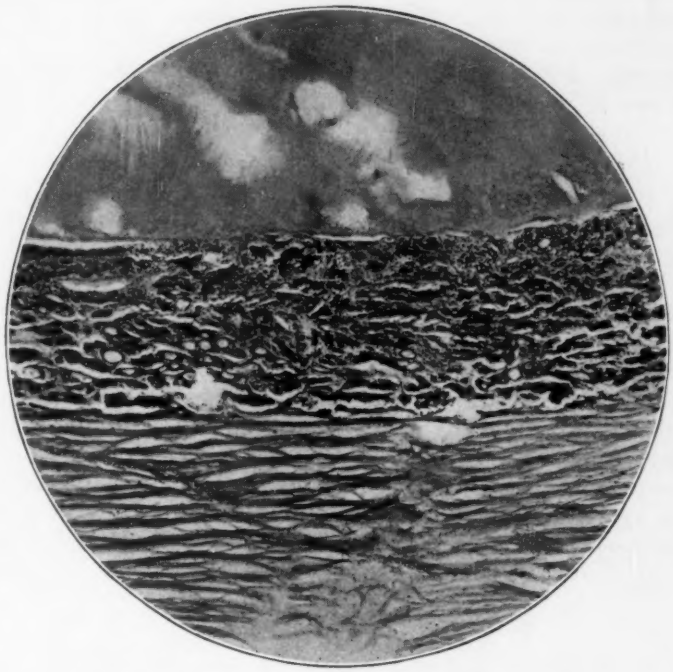

Fig. 9.—The choroidal tumor, right eye (× 26).

as Suker and Grosvenor,[6] Knapp,[15] McDannald and Payne,[28] Benedict,[9e] Davis [9f] and others [9] have shown, the metastasis may be in the optic nerve or ciliary body.

When the typical changes are discovered carcinoma should be suspected, and when evidence of carcinoma elsewhere in the body is or has been present, metastasis must be considered until excluded by further study of the patient.

It is interesting to refer to the question of hemorrhage, for some authors have spoken of it as a precursor of extension and some have even suggested that they have seen an individual embolus.

It will be noted that in the case here reported the patient had several hemorrhages, but that there was no evidence of any special increase in activity following their appearance. It must also be emphasized that there was marked change in the caliber of the arteries with attendant hyperpiesia.

There is every reason to expect an increase in the number of cases of metastatic carcinoma of the choroid. It may be that irradiation will prolong the seeing days of the patient. Carcinoma must be differentiated from sarcoma, which is a primary growth and jeopardizes the life of the patient if the eye is not enucleated. Most frequently sarcoma is circumscribed and projects forward, with comparatively early secondary glaucoma. This is in contrast to carcinoma, in which the patient is already condemned to death and removal of the eye has no influence either in hastening or retarding demise. Typical carcinoma spreads laterally with little tendency to increase in thickness. Some of the more malignant lesions are grayish and others are yellowish pink or pale yellow, so that the color in itself is not diagnostic. In several cases carcinoma of the choroid has been reported before the primary growth was discovered.

Clinicians must be careful not to subject the patient to an unnecessary operation; enucleation does not stop the extension from the primary growth and the eyeball should not be removed unless it is the site of uncontrollable pain. I do not, however, subscribe to the view that the removal of the eyeball hastens death. It certainly did not in the case here reported.

CONCLUSION

This case is unique because it is the only one which has been recorded by colored photographs from an early stage to death. It is also unusual because the photographs clearly show the development of a fresh metastasis in the left eye, which was neither accompanied by demonstrable change in the circulation over the site of the lesion nor caused by an embolus so far as could be detected.

A satisfactory colored photograph is most instructive and of great value in the correct diagnosis.

In every case of extensive carcinomatosis an ophthalmoscopic examination should be made so that eventually some worth while statistics can be compiled.

Metastatic carcinoma of the choroid is rare; few ophthalmologists ever encounter more than one case in their private practice. It is essential for this reason that all diagnosticians appreciate the possibility of ocular metastasis, and, further, it must be remembered that such metastasis may be discovered before the primary growth.

344 State Street.

DISCUSSION

DR. ARNOLD KNAPP: I saw this patient on Nov. 21, 1938. The condition was interesting for the following reasons: There were two areas, one in each eye. One was a large, circumscribed, rounded area of choroidal change in the temporal side of the fundus of the right eye. It looked intensely white, like an area of choroidal atrophy with irregular pigmentation, and the retina over it showed only + 2 elevation. The area in the other eye was smaller but similar, and it was situated directly above the optic nerve. This also was only slightly elevated. These areas were entirely different from the usual picture of metastatic carcinoma of the choroid, in which the growth is not sharply defined, is pale gray with grayish mottling and has more marked elevation. I suggested that a roentgenologic examination of the mediastinum be made, because I have never seen a metastatic growth of the choroid when there was not also a lesion of the mediastinum if the process was secondary to a cancer of the breast.

DR. DANIEL M. ROLETT: Several months ago I saw a man of 56 or 57 with sudden loss of vision in his left eye. He had already been told that he had a retinal detachment and wanted confirmation of the diagnosis. I did find a flat retinal detachment with yellowish brown pigmentation similar to that shown by

Dr. Bedell. It looked to me like a malignant process, and I had the patient enter the hospital for further study, as a result of which I decided to do an exploratory paracentesis. A small needle was inserted into the eye in the approximate area of the detachment, and a brownish hemorrhagic fluid was removed. A few days later the patient suffered considerable pain in the eye. Enucleation was advised, and he consented to the operation. Dr. Samuels sent me a detailed histologic report of carcinoma. A section of the eye was also sent to the Memorial Hospital for the Treatment of Cancer and Allied Diseases, which subsequently reported metastatic carcinoma. On examination it was found that the patient had tumor involvement of the lungs, a complication to which Dr. Knapp referred, and of the thyroid, as well as primary involvement of the left kidney.

Dr. Arthur J. Bedell: Many of the cases reported in the literature were observed only after the retina had become detached. It was for this reason that the pictures were shown, to make recognition of the early appearance of the lesion possible.

CONGENITAL PARALYSIS OF LATERAL ROTATORS OF EYES WITH PARALYSIS OF MUSCLES OF FACE

AVERY M. HICKS, M.D.
SAN FRANCISCO

Congenital bilateral paralysis of the muscles which move the eyes in the horizontal plane and congenital bilateral paralysis of the muscles of the face occasionally occur together. This disabling congenital anomaly makes up a small group of congenital defects which probably is a step in the transition from certain forms of congenital absence of abduction and the congential ophthalmoplegias. It was first described by Albrecht von Graefe (1875), and later by Harlan (1881), Chisolm (1887), Möbius (1888) and Schapringer (1889). Each of these authors added slight variations to the original description. Heubner (1900) published the results of an anatomic examination of a patient who came to autopsy. There was hypoplasia of the brain stem in the area of the sixth and seventh cranial nerves. The anomaly is frequently spoken of as Möbius' syndrome, because of that author's exact and detailed descriptions and discussions of the disease in 1888 and 1892.

The principal symptoms of this congenital anomaly are as follows: 1. Either all four lateral rotator muscles are totally paralyzed, or only the two abductor muscles are totally paralyzed while the two adductor muscles are only paretic. The response of the medial rectus muscles to the innervation of convergence is occasionally normal but is usually diminished. The contractions of these muscles to the convergence innervation is always more active than their response to innervation for associated movements. 2. Both facial nerves are either paralyzed or paretic to some degree. Frequently one side is more affected than the other. Other congenital defects are frequently found in persons with this anomaly.

Congenital absence of abduction is a more common anomaly of the ocular muscles. The cardinal symptom of this condition is an absence of abduction of the affected eye past the midline. Weakness or absence of adduction, weakness of convergence and retraction of the eyeball and narrowing of the palpebral fissure on the impulse for adduction are frequently found as symptoms accompanying the abscence of abduction. This defect is caused either by a fibrosis of the lateral rectus muscle or by a maldevelopment of the lateral rectus muscle because of absence of a nerve supply or absence of the development of the muscle tissue or both. When the lateral rectus muscle has been replaced by fiber tissue, the histologic changes in the ocular muscles are similar to changes observed in muscles which have undergone fibrosis, as in Volkmann's ecchymotic contracture. Because of this similarity and the fact that various types of trauma to the head do occur during the passage of the head through the birth canal, it seems possible that the fibrosis in the ocular muscle might be due to ecchymosis from pressure of some irregularity or deformity of the birth canal. When abduction is absent because of lack of nervous supply to the lateral rectus muscle or because of absence of the muscle, the defect is a true developmental defect.

Another uncommon defect of lateral rotation is weakness of both abduction and adduction in combination with normal vertical movements of the eyeballs and normal functions of the muscles of the face. In fact, there is probably a gradual

From the Division of Ophthalmology, Stanford University Medical School.

transition from the so-called normal extraocular motor apparatus to the presence of all the signs of Möbius' syndrome.

I should like to report 4 cases of Möbius syndrome which have come under my observation in recent years and review the theory advanced to explain this anomaly.

CASE 1.—T. B., an Italian boy aged 12, was brought to the clinic at Children's Hospital because the right eye was painful and red. Examination showed the cause of the symptoms to be a small corneal ulcer at about 6 o'clock near the limbus, which was probably caused by poor closure of the eyelids during sleep. The facial appearance was striking. The skin of the face was smooth and masklike, and all the soft tissues sagged in a manner similar to that seen in a person who has suffered total paralysis of the facial nerve. This appearance was said to have been present since birth. The upper eyelids were shortened, and there were no lid folds or wrinkles in the skin. There was a pronounced ectropion of each lower eyelid, with exposure of the conjunctiva and eversion of the papilla lacrimalis. There was no movement or change in the position or appearance of the lids on the impulse to close the eyes. The innervation, however, did produce a typical Bell phenomenon, so that the corneas moved upward practically out of sight under the upper lids. The boy could not wrinkle his forehead, whistle or smile. There was total bilateral paralysis of all the muscles of the face innervated by the facial nerves. The uncorrected vision was 20/25 in each eye, and with a relatively weak spectacle lens to correct the compound hyperopic astigmatism, the vision was 20/20. The conjunctiva of the lower lids was red and hypertrophied. The corneas were normal except for the small ulcer on the right, which healed in a few days. The anterior chambers were clear and of normal depth. The irises were normal, and the pupils were equal and regular and reacted normally to physiologic stimulation. The lenses and media were clear, and the fields of vision and the fundi were normal. In the primary position for distant fixation there was orthophoria, and at the near point there was 16 prism diopters of exophoria. The near point of convergence measured 220 mm. from the bridge of the nose. There was no lateral rotation of either eye when the patient was directed to look to the right or left. Whenever he wanted to look sideways he would turn his head in the desired direction. When the head was fixed and he was encouraged to make a great effort to look to the right or left, a slight lateral rotation could be seen. This movement was always accompanied by a narrowing of the pupils, which suggested that it was the result, in part at least, of a convergence innervation. There was no spontaneous diplopia, but diplopia could be produced with a red glass and a vertical prism. The two images were directly one above the other in the primary position. A low degree of exophoria developed when the plane of vision was elevated and a low degree of esophoria when it was depressed. There was some limitation of the vertical movements of the eyes. Vestibular stimulation by the turning and caloric tests did not create any nystagmus. The boy probably could have been helped by a plastic operation on the lids to reduce the size of the palpebral fissures. This would have resulted in better protection for the corneas. After the corneal ulcer healed, he disappeared from observation, and frequent inquiries failed to encourage him to return to the clinic.

This case is an example of total paralysis of all the muscles of the face, total absence of lateral rotation of the eyes on impulse for associated movements and a weakness of convergence. The small amount of lateral rotation noted under certain examining conditions was probably the result of a convergence innervation.

Congenital absence of abduction with or without retraction shows little if any tendency to be hereditary,[1] while congenital ophthalmoplegia is commonly found in several members of the same family. Paralysis of lateral movements associated with other congenital anomalies of the ocular muscles, such as pronounced overfunction of the inferior oblique muscle or paralysis of some of the vertical muscles, is usually considered as constituting an intermediate form between congenital ophthalmoplegia and congenital absence of abduction and frequently shows a hereditary tendency. Congenital bilateral paralysis of the muscle producing lateral rotation accompanied by bilateral paralysis of the muscles of the face probably

1. Chavasse said that this condition is hereditary. Bielschowsky's report of 68 cases disclosed no hereditary tendency. I reviewed the cases observed at Stanford University Medical School Clinic and Children's Hospital, and private records revealed no familial or hereditary tendency.

constitutes another intermediate form and also shows a hereditary tendency. This fact is illustrated by the following 2 cases, those of a mother and her child.

CASE 2.—When first seen, in 1934, A. C., a boy, was 9 months old. The mother stated that his eyes had been crossed and fixed at the internal canthus since birth. She had noticed that his face was smooth and lacked expression. A supernumerary thumb and web fingers had been treated surgically soon after birth. Examination showed that the baby was well nourished and well developed, with a smooth, masklike face, and did not completely close his eyes. The eyes were more or less fixed at the nasal canthi. The child was seen frequently during the next few years, during which time the left eye remained fixed at the internal canthus. One could occasionally observe a slight, clumsy lateral rotation of the right eye from its usual position at the internal canthus. The child developed mentally very slowly and at the age of about 4 years was found to be deaf. Because of his inability to cooperate, it was difficult to estimate the presence or absence of convergence movements as well as the extent of the vertical rotations of the eye. It was noted, however, that when he attempted to close his eyes, there was some movement of the eyelids, and the eyeballs rotated upward under the upper lids (Bell's phenomenon).

As mentioned, there was a strabismus in this case. In many cases of Möbius' syndrome strabismus is not present, but the factors which normally produce it may be superimposed on the anatomic anomalies characteristic of Möbius' syndrome, and thus when the two exist together, the picture is like that described. The presence of such congenital defects as web fingers, supernumerary digits and deafness are commonly associated with this congenital anomaly. I believe that this is a case of bilateral congenital absence of abduction with bilateral paralysis of the face in spite of the fact that I have not been able to prove the presence of all the typical signs of the disease. The involvement of the sixth, seventh and eighth cranial nerves suggests some pathologic process affecting the brain stem at the level of their origin.

Pronounced convergent strabismus with an eye that seems to be fixed at the internal canthus in a young baby should not be diagnosed immediately as absence of abduction. The child should be observed until he reaches an age at which an adequate examination of the ocular rotation can be made. During the interval one eye should be kept bandaged except during short periods in which the bandage is removed for examination of the ocular motility. Often the anomaly is not absence of abduction but hypertrophy and hyperplasia of the medial rectus muscles with normal or slightly attenuated external rectus muscles. The treatment of the two types of anomaly is surgical, but because of the necessity of a different surgical procedure for each, an exact diagnosis is desirable.

CASE 3.—The child's mother, Mrs. A. C., was 27 years old. She had never suffered from asthenopic symptoms but knew that her eyes did not move like those of most people. She also knew that her face was smooth, that she had difficulty in smiling, that she had never been able to whistle and that her eyes watered whenever she was out in the wind. Her vision was 20/20 in each eye. Her face lacked expression and she could not wrinkle her forehead. Her eyes were deeply set and the palpebral fissures narrow. There was slight ectropion of the lower lids, so that the puncta were everted. When she blinked or attempted to close the eyelids, there was a slight downward motion of the upper lids, and at the same time the eyeballs rolled up under the lids, showing an active Bell phenomenon. There was total absence of lateral rotation of the eyeballs, but the vertical movements of the eyes were essentially normal. When an object was moved from a distance toward the eyes, the eyes maintained binocular fixation up to about 90 mm., which is a relatively normal converging power. The movements of the eyes in response to the compulsion to fusion were also essentially normal. When one eye was held closed, a small amount of lateral movement could be demonstrated in the open eye. This movement, however, was not due to an impulse for associated lateral movement, but to an impulse to convergence, as there was a narrowing of the pupil on adduction and a widening of the pupil as the eye returned to the primary position. If the patient fixed an object held in the midline and then half closed the right eye, and one moved the object slowly to the right, the left eye made a small degree of lateral rotation in the sense of adduction to maintain fixation. If the right eye was observed through

the narrow palpebral fissure, it was found to make a slight movement of adduction when the left eye followed the object of fixation as it was moved from left to right. These movements were accompanied by a narrowing of the pupils. After a little training, the patient could follow the object of fixation with either eye. With every movement of adduction of the fixing eye, there were a disjunctive movement of the nonfixing eye, a rotation of the nonfixing eye about the line of sight, a narrowing of the pupil and an increase in the amount of hypermetropia. The whole of the lateral movement of the eye was due to impulses to convergence and not to impulses of associated lateral movement. No nystagmus resulted from vestibular irritation by either the caloric or the turning test. The hearing was normal.

This case is an example of Möbius' syndrome in which the facial nerve has retained a few fibers, which have prevented the sagging of the face seen in case 1.

Congenital anomalies other than those of the muscles of the eyes and face frequently accompany this syndrome, while congenital anomalies are relatively uncommon among patients who suffer from a unilateral congenital absence of abduction. In case 2 there were supernumerary thumbs, web fingers and deafness as well as paralysis of the muscles of the face and absence of lateral rotations of the eyes. Other congenital defects which have been reported as accompanying this disease are deformity of the ears; absence of hands, fingers or feet; defects of the muscles of the chest or neck, and defects of the musculature of the tongue.

CASE 4.—A 9 year old boy was brought to Stanford University Medical School Clinic because a small growth had been noted near the limbus on the temporal side of each eyeball. These were typical dermoid cysts, which frequently are found at this location. The child's face was smooth, the forehead could not be wrinkled and he could not whistle. The eyelids could be closed but not squeezed together. There was pronounced limitation of lateral rotation of both eyes. Although there was a convergent strabismus of 5 to 10 degrees, there was a marked weakness of convergence. The vertical movements of the eyes were also restricted. The two dermoid cysts were removed, and after the wounds had healed satisfactorily, the medial two thirds of the superior and inferior rectus muscles were transplanted to the insertions of the external rectus muscles. The medial rectus muscles were not set back, as it was felt that any interference with these muscles would only increase the weakness of convergence. The same technic was used for the two eyes, there being an interval of two months between operations. The end result was satisfactory as far as the position of the eyes was concerned, but the operations failed to make possible any movement of abduction past the midposition. The superior and inferior rectus muscles appeared normal in size and texture. The lateral rectus muscles were thin and attenuated and lacked tone, but they appeared to contain some normal muscle fibers. The external rectus muscles were not fibrous and nonelastic, as they frequently are in cases of congenital absence of abduction.

The exact nature and site of the lesion which produces Möbius' syndrome are not known. It is probable that the site, nature and extent of the lesion are somewhat different in various cases. In those cases in which nystagmus is absent on vestibular stimulation and there is a response of the medial rectus muscle to impulses of convergence but not to impulses for associated movements, as in case 3, the lesion probably interferes with the continuity of the fibers of the posterior longitudinal fasciculus, so as to prevent the impulses originating in the vestibular apparatus from reaching the nucleus of the third nerve. This nucleus and the fibers to the medial rectus muscle must be intact, for otherwise convergence would be impossible. The lesion is probably at the level of the nuclei of the sixth and seventh nerves but may extend above and below the level of these centers. In case 3, that of the baby with impaired hearing, the disease process was probably more extensive and impaired the function of the nucleus of the eighth cranial nerve also. In case 4, that of the boy with poor convergence and a weakness of the upward and downward rotations, the disease process had probably extended upward to involve a portion of the third nerve nucleus.

Several theories have been advanced to account for the nature of the disease process which produces this clinical picture. The best known are Möbius' theory

of intrauterine nuclear disease, Kann's theory of congenital aplasia of part of the brain stem and Hübner's theory of hypoplasia of the brain stem. Hübner based his theory of hypoplasia on the anatomic examination of the brain stem of a 19 month old boy who showed a complete bilateral absence of abduction with paralysis of the muscles of the face. The involvement of the facial musculature was more pronounced on the left side, and there was an atrophy of the left half of the tongue. Postmortem examination disclosed marked defects in the motor ganglions and nerve fibers in the medulla and the pons. There were practically no cells in the nuclei of the facial, hypoglossal and abducens nerves. There were no signs of degeneration or inflammation, and therefore Hübner concluded that the defect was due to hypoplasia. The clinical phenomena do not offer any basis on which to judge the value of these theories; in fact, it is not possible to determine whether the anatomic muscular anomalies found represent primary or secondary changes. Thus one must conclude that this congenital anomaly is due to a pathologic process of an unknown nature involving the brain stem.

490 Post Street.

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ABSORPTION OF INFRA-ROENTGEN (BUCKY) RAYS OF VARIOUS QUALITIES BY THE ANTERIOR PORTIONS OF THE EYEBALL

F. SAGHER, M.D.
AND
E. SAGHER, M.D.†
JERUSALEM, PALESTINE

Infra-roentgen rays have been used in the treatment of diseases of the anterior portions of the eyeball and conjunctiva by Krasso,[1] Monyukova and Serebryaniy,[2] Mylius,[3] Rosamoely,[4] Baltin and Serebryaniy [5] and others. Krasso, in a number of articles reported beneficial results in various ocular diseases with this therapy, for example herpetic corneal disease, superficial punctate keratitis, dendritic keratitis, filamentous keratitis, superficial infiltrations and ulcers and episcleritis. On the other hand, no success was observed by this author (or by Gnad [6]) in parenchymatous keratitis. They used doses of from 70 to 150 roentgens with one to five exposures and half value layers of 0.020 and 0.025 mm. of aluminum but pointed out that rays of the former quality produced better results.

Recently Pfeiffer [7] reported on a sufficiently large material. He had treated 302 patients with a total of 1,200 exposures during the preceding five years. Beneficial

From the Dermatologic Department (head, Dr. A. Dostrovsky), Rothschild-Hadassah-University Hospital.

† Dr. E. Sagher, who took an active part in the experimental work, died before the results could be published.

1. Krasso, J.: (*a*) Die Beeinflussung d. Glaukoms durch Bestrahlungen mit Bucky's Grenzstrahlen, Ztschr. f. Augenh. **69**:74, 1929; (*b*) Anwendung und Dosierung von Bucky's Grenzstrahlen in der Augenheilkunde, Strahlentherapie **38**:358, 1930; (*c*) Durch Bucky's Grenzstrahlen guenstig beeinflusster Fall von Acne rosacea, Klin. Monatsbl. f. Augenh. **84**: 853, 1930; (*d*) Experimentelle und histologische Untersuchungen ueber den Einfluss einer einmaligen Bestrahlung mit Bucky's Grenzstrahlen auf das gesunde Kaninchenauge, Ztschr. f. Augenh. **70**:237, 1930; (*e*) Die Behandlung der Erkrankungen d. vordern Bulbusabschnittes mit Bucky's Grenzstrahlen, ibid. **71**: 1 and 101, 1930; (*f*) Grenzstrahlentherapie der Conjunctivitis acuta und chronica catarrhalis, ibid. **75**:285, 1931; (*g*) Klinische und histologische Beitraege zur Kenntnis der tiefen Wirkung von Bucky's Grenzstrahlen am Auge, ibid. **75**: 32, 1931; (*h*) Ueber boesartige Randgeschwuere der Hornhaut (Abortive Formen d. Ulcus rodens) und deren Beeinflussung durch Grenzstrahlen, ibid. **77**:182, 1932; (*i*) Les rayons-limites en ophthalmologie, J. de radiol. et d'electrol. **16**:117, 1932; (*j*) Grenzstrahlenthubus zur Bestrahlung d. Auges, Strahlentherapie **43**:190, 1932. Krasso, J., and Loeffler, A.: Ueber den KCA-Gehalt des Blutes bei Glaukomkranken und seine Beeinflussung durch Grenzstrahlen, Arch. f. Augenh. **106**:255, 1932.

2. Monyukova, N. K., and Serebryaniy, Z. M.: Die Anwendung der Bucky-Grenzstrahlen bei äusseren Augenerkrankungen, in Special Collection on Ophthalmology in Honor of Forty Years of Scientific Activity of M. I. Averbakh, Moscow, Gosudarstvennoe izdatelstvo biologicheskov i meditsinskoy literatury, 1935, p. 291.

3. Mylius, K.: Wirkung von Bucky-Strahlen (Grenzstrahlen) auf das Auge, Ztschr. f. Augenh. **64**:316, 1928.

4. Rosamoely, L.: Les rayons mous en ophthalmologie, Rev. de physiothérap. **13**:20, 1937.

5. Baltin, M. M., and Serebryaniy, Z. M.: Infra-Roentgen Rays in Therapy of Herpetic Keratitis, Vestnik oftal. **10**:688, 1937.

6. Gnad, F.: Ueber den Erfolg der Roentgen-und Buckystrahlentherapie bei Keratitis parenchymatosa, Klin. Monatsbl. f. Augenh. **89**:446, 1932.

7. Pfeiffer, R. L.: Treatment of Diseases of the Eye with Grenz Rays, Arch. Ophth. **21**:976 (June) 1939.

results were recorded, particularly in corneal ulcers, episcleritis, scleritis and vernal conjunctivitis. He recommended giving 452 r with a half value layer of 0.024 mm. of aluminum twice weekly up to a total of five exposures. In urgent cases, the patient should be treated every day or every second day.

The same author is responsible for the first data concerning overdosing with infra-roentgen rays. Four patients who received four series of five exposures each (452 r) at intervals of two weeks showed remarkable reactions of the conjunctiva and the episcleritic tissue "manifested by increased engorgement of the vessels and pain." None showed destruction of the cornea or lens. Pfeiffer [7] drew attention to the special advantage of treatment with infra-roentgen rays over other methods, pointing out that it is easily administered and in itself painless; indeed, it produces an analgesic effect. Inflammatory symptoms are rapidly influenced, with no undesirable side effects, and ulcers, episcleritis and scleritis are most amenable to this kind of therapy, a great proportion of the patients being actually cured.

In dystrophic conditions, as a rule no results were obtained. Pfeiffer therefore concluded that infra-roentgen rays are particularly effective in the treatment of superficial processes of the eyeball, more effective than any other kind of radiation. He prophesied a great future for this therapeutic agent.

Bucky,[8] discussing these results, suggested that treatment with infra-roentgen rays be employed only for superficial tumors of the eyeball and the eyelids, for which, he stated, it is the treatment of choice. He recommended two to five exposures of from 1,500 to 2,500 r at proper intervals.

Although in our opinion these rays should not be applied to even the most superficial epithelioma of the skin, since it is impossible to foresee whether recurrences will develop from deeply buried islets, and roentgen ray or radium treatment is the more logical procedure, the region of the eyes and eyelids should be considered an exception to this rule. Here roentgen rays and radium, with their greater penetrating power, although more reliable as to the effect obtained, constitute a far greater danger to the eyeball.

The therapeutic attempts cited were preceded by experiments on rabbits reported by Erggelet,[9] Krasso [1] and Miyahara.[10] These authors subjected eyes of rabbits to the action of infra-roentgen rays in one or several exposures and the resulting reactions were followed up by gross and histologic examinations. Erggelet [9] did not observe any kind of injury to the lens, even when the treatment was continued for two and one-half years (the single doses given were 150 r with a total of 1,800 r, in twelve exposures within one hundred eighty-six days, or a total of 8,360 r in single doses of 440 r), the period of observation being one year and ten months after the treatment had been terminated.

Krasso [1] observed the occurrence of conjunctival lesions in his experimental rabbits only after application of as much as 7,830 r, and lesions of the corneal epithelium only in animals which had been given 4,000 to 6,159 r, and these lesions disappeared completely. After application of 7,830 r regeneration took place but even after two hundred and twenty-four days the histologic picture had not returned to normal, although clinically the eye could be considered normal after ninety-nine

8. Bucky, G.: Grenz Ray Therapy, New York, The Macmillan Company, 1929.

9. Erggelet, H.: Zur Frage der Strahlenwirkung am Auge, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **48**:245, 1930.

10. Miyahara, H.: Experimentelle Untersuchungen ueber den Einfluss einer einmaligen Bestrahlung mit Bucky's Grenzstrahlen auf das gesunde oder verschieden vorbehandelte Kaninchenauge, Acta Soc. ophth. jap. **36**:564 and 612, 1932; Bestrahlungsversuche mit Grenzstrahlen gegen Kaninchensarkom, ibid. **36**:609, 1932.

days. Lesions of the lens or iris were not encountered in any animal. Iritis, of short duration, was observed in only 1 animal; it occurred, without a lenticular lesion, after seven months.

Miyahara [10] exposed the eyes of his experimental animals (white as well as pigmented rabbits) to the action of these rays in one or several sessions. The treatment was applied to both normal and aphakic eyes and to inflamed eyes; it was given immediately after aspiration of the contents of the anterior chamber as well as after instillation of solution of atropine, pilocarpine, physostigmine, epinephrine, cocaine and zinc sulfate. In some instances opaqueness of the cornea, which, however, disappeared later, or suppurative conjunctivitis was recorded. Another paper by the same author dealt with the influence of infra-roentgen rays on sarcoma grafted into rabbits' eyes. After application of 908 r to a tumor its growth was temporarily suspended, while a sarcoma which had been treated with 20,432 r continued growing.

Gasteiger [11] discussed the effect of infra-roentgen rays on bacterial pathogens of the eye, having observed that in cultures such germs are not destroyed by 50 to 5,000 r. He held that the definite improvement recorded in a case of serpent ulcer must have been produced by action of the rays on the tissues and not on the germs themselves.

In Thompson, Pfeiffer and Gallardo's [12] papers the problem of the formation of antibodies in the cornea as a result of infra-roentgen radiation was dealt with. The experimental procedure of these authors was to introduce purified egg protein into the cornea of a rabbit, exposing it subsequently to the action of infra-roentgen rays. The effect was greatest if irradiation was performed eight days previous to the introduction of the material into the cornea. The irradiated cornea subsequently contained greater amounts of precipitins than the untreated one, the titer being roughly twelve times as high. The same authors discussed the influence of infra-roentgen rays on experimentally produced infections of the eyes of rabbits. Lesions were produced in both eyes by intracorneal inoculation of staphylococci, and only one eye was treated with infra-roentgen rays. Treatment was given in one group of animals before and in another after the introduction of the staphylococci into the eyes. In the eyes not previously treated, severe intraocular lesions developed and in 1 animal corneal perforation. Panophthalmia was observed on the untreated side in 2 animals. In the treated eyes, the reactions to the inoculation, if any, were far less severe and there was no instance of panophthalmia. A conjunctival reaction, as a matter of fact, appeared in both eyes, but in the eye which had been exposed to the rays suppuration disappeared much more rapidly. The difference between the treated and the untreated eyes was four times as great as the standard error.

Before applying the results of these experiments to human subjects, it seemed to us of particular importance to study first the permeability of the anterior portions of the bulb to infra-roentgen rays. These rays constitute a mixture the half value layer of which is between 0.014 and 0.035 mm. of aluminum. The rays usually used in dermatologic therapy are those with half value layers between 0.020 and 0.033 mm. The harder types (over 0.030 mm.) are obtained by inserting filters (we used cellophane filters).

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11. Gasteiger, H.: Ueber die Wirkung von Bucky's Grenzstrahlen auf augenpathogene Keime, Arch. f. Augenh. **104**:399, 1931.

12. Thompson, R.; Pfeiffer, R., and Gallardo, E.: Stimulation of Local Antibody Formation in the Cornea by Grenz Rays, Proc. Soc. Exper. Biol. & Med. **36**:179, 1937. Gallardo, E.; Pfeiffer, R., and Thompson, R.: Infra-Roentgen Treatment of Experimental Infection, Am. J. Ophth. **23**:41, 1940.

Only two concise reports are as yet available dealing with the question of the permeability of the anterior portions of the eyeball to infra-roentgen rays. Krasso [1] established the rate of absorption of fresh corneas of rabbits to be 79.94 per cent and that of the iris and the aqueous humor of the anterior chamber to be 97.27 per cent of the surface dose.

At a meeting of the "Oculists of Central Germany," Erggelet [9] reported on experiments on corneas of rabbits and of human beings with rays having half value layers of 0.016 and 0.018 mm. He found the proportion of rays which were not absorbed (with a thickness of cornea of roughly 1 mm.) to be one tenth. That no lesions occurred in the lenses of the rabbits within the following two years was explained by this author as being due to the fact that as the distance from cornea to lens was 7 mm. the latter received but 1/10,000,000 of the original dose. When roentgen rays are used, cataract develops even after 1 skin erythema dose (550 r). It would appear that because of lack of blood vessels in the lens a cumulative effect of repeated small doses of roentgen rays occurs, although this may be manifest only after two or three years. We have, however, no information as yet on the delayed cumulative effect on the lens, and possibly on the cornea, of infra-roentgen rays.

Great progress has been made in infra-roentgen ray therapy since the first experiments were carried out. Today there is nothing extraordinary in working with gaged bulbs and to have at one's disposal the entire range of ray qualities. In the various therapeutic experiments all sorts of different doses and qualities have been used, but no information has so far been presented on the extent to which the various portions of the eyeball are permeable to infra-roentgen rays. Qualities represented by half value layers ranging from 0.014 to 0.031 mm. of aluminum were studied without absorption curves or data, and the sclera was not included in any of the considerations. This, in our opinion, is absolutely unjustified, since behind the scleral tissue the protecting aqueous humor is absent, the lens is nearer and the ciliary body (the reaction of which, as the vascularized part, is of greatest significance) is interposed between the two organs. If, for instance, ulcers of the corneal limbus are exposed to the rays (Krasso [1]), the sclera receives the direct beam, so that its particular absorptional conditions should not be neglected.[13]

Absorption data for various materials were given by Bucky,[8] who pointed out that with 10 kilovolts 50 per cent of the rays are absorbed by layers of 0.47 mm. of water, 0.52 mm. of muscle or cutis vera, 0.56 mm. of epidermis and 0.77 mm. of subcutaneous tissue. He did not include data concerning the sclera or cornea.

We were particularly interested in the problem of whether the anterior portions of the eyeball may be exposed to high doses without damage to themselves or to the organs situated beneath them, for example, the lens, ciliary body or iris. This seemed particularly important because of the necessity for irradiation of superficial tumors and granulation tissue, for example leprous infiltrations of the ciliary body. We irradiated lepra of the skin by fractional exposures to infra-roentgen rays up to a total of 5,000 r. The infiltrations disappeared, and, surprisingly, new eruptions, which appeared after one and one-half years, did not attack the regions which had previously been exposed to the rays. The experiments were

13. After our studies were completed, an article was published by P. Dethmers and P. H. Boshoff (Grenz Rays and Their Application in Ophthalmology, Arch. Ophth. **24**:656 [Oct.] 1940), dealing with similar problems, in which for the first time data on the permeability of the sclera (in pigs) were given. In the experiments reported, however, half value layers of no more than 0.020 mm. were used. The authors established the rate of absorption for the human cornea as 90 per cent, while for the various parts of the sclera it was given as 73 to 83 per cent. We were unable to verify their statement that the aqueous humor absorbed 100 per cent of the rays.

undertaken on 2 leprous patients in about ten different localizations and invariably had the same result. As no effective method has so far been discovered for the treatment of leprous infiltrations of the sclera and the prevention of blindness, it seemed to us of greatest importance to learn whether such doses might be applied to the eyes. There was, on the other hand, the question of what percentage of rays—with small doses—would penetrate the cornea and sclera, and, if they were directed onto the lateral portions, get beyond the sclera and affect the ciliary body and then lens (the lens being known to show lesions years after several exposures even to very small doses of rays).

In view of the results obtained in the experiments, previously cited, on the eyes of living rabbits and the fact that the maximum dose which could safely be given without damage had been established with reference to the cornea, we studied the permeability of the various qualities of infra-roentgen rays available.

Our determinations were carried out with the Siemens infra-roentgen ray apparatus combined with an ionognom.[14]

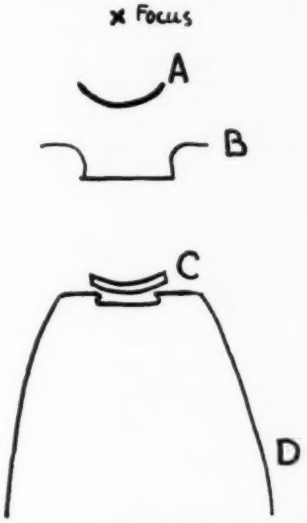

Fig. 1.—Diagram showing the procedure employed: *A*, Lindenmann window; *B*, tube; *C*, cornea or sclera; *D*, ionognom.

14. The ionognom was developed on the basis of the hammer dosimeter (Uhlmann, E., and Pychlau, H.: Ueber ein neues Messinstrument für Roentgenoberflaechentherapie, Strahlentherapie **47**:738, 1933). It consists of a pyramid-shaped box holding a meter chamber and a container with a stopwatch. These parts are connected by wire. Inside the ionization chamber an electrode is inserted which is connected with two electrometer plates. The connection with the stopwatch makes it possible to measure the time necessary for charging the electrometer. For the purpose of control, a radium preparation is mounted on a slide opposite the point of entrance. The instrument can be used for the entire series of infra-roentgen rays, its standard gage being 45 r. It allows the quantities of rays to be read in a simple manner. Qualitative determinations are made by first determining the time shown by the stopwatch without filtration and then inserting an aluminum filter. The thickness of the filter in connection with which the time is twice as great as the original period represents the half value layer of the rays being measured. The distance between the meter chamber and the focus was 10 cm. With the automatically operated stopwatch, which was connected with the ionognom, the time between two successive dose signals was determined.

(Footnote continued on next page)

With this experimental setup we studied the absorptive qualities of the tissues under consideration for the entire range of ray qualities used by us clinically (with half value layers between 0.019 and 0.033 mm. of aluminum). The results are shown in table 1.

We examined corneas and scleras of rabbits and of human beings. According to Cipollaro and Mutscheller,[15] live tissue shows more or less the same rate of absorption as dead tissue.

Indeed, in some respects the use of dead material is even more advantageous, since the tissue remains unchanged. With live tissue, each specimen can be used for only one experiment, since otherwise the large quantity of rays applied would, as in the skin, alter the sensitivity, the humidity and the permeability to rays. In Halberstaedter's [16] comprehensive study on the subject, dealing with the biologic reactions of the skin after roentgen ray treatment, the problem of increased sensitivity received due consideration. Although the increase in sensitivity of the tissue probably does not directly affect its permeability, the associated change in humidity in such experiments most likely does.

TABLE 1.—*Irradiation Produced with 6 to 14 Kilovolts Peak* *

Number of Experiment	Half Value Layer, Mm. of Aluminum	Skin-Focus Distance, Cm.	Milliamperes	Volts	Roentgens	Seconds	Filter	Roentgens per Minute
1	0.019	10	10	160	100	20	...	300
2	0.021	10	10	170	100	16	...	375
3	0.023	10	10	180	100	14	...	428
4	0.025	10	10	200	100	11	...	545
5	0.027	10	10	210	100	9	...	666
6	0.030	10	15	210	100	7	...	857
7	0.033	10	15	210	100	9	Cellophane, 0.01 mm.	666

* We used fine aluminum foil placed at our disposal by Dr. Goldhaber (Cancer Research Institute of the Hebrew University, Jerusalem). The time was measured previous to and after insertion of the tissues to be examined (which procedure was repeated several times). Then, according to the formula described, the average percentage of absorption was calculated. Detailed protocols would exceed the scope of this article.

To begin with, we measured the permeability of the cornea and sclera in rabbits (fig. 2). We used for this purpose freshly enucleated eyes with no fixation. To prevent evaporation, which might affect the results of the experiments, we moistened

In accordance with the standard gage of our instrument, the dose was 45 r. The intensity (roentgens per minute) of the rays was calculated from the formula $J = \frac{K}{T}$, K being the standard gage of the instrument (45 r) and T the time read from the stopwatch in minutes. Owing to the absorption taking place in the interposed material, the length of time must necessarily be increased. If without filtration the intensity equals J_1 and the corresponding period of time T_1, and if with a filter the values are J_2 and T_2, the percentage of penetrating rays is calculated from the formula:

$$\text{percentage} = \frac{J_1}{J_2} = \left(\frac{k}{T_1} : \frac{K}{T_2}\right) \times 100$$

$$\text{percentage} = \frac{T_2}{T_1} \times 100$$

In our experiments the procedure was to introduce the organs and to read the time previous to and after their introduction (fig. 1).

15. Cipollaro, A. C., and Mutscheller, A.: Absorption of Roentgen Rays by Skin: Experimental Determinations, Arch. Dermat. & Syph. **41**:87 (Jan.) 1940.

16. Halberstaedter, L.: Allgemeine biologische und schaedigende Wirkungen d. Roentgenstrahlen, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 5, pt. 2.

the detached portions of tissue with aqueous humor at intervals or placed them in physiologic solution of sodium chloride and after the fluid had been removed continued the experiments.

In order to determine the amount of rays delivered to the lens, we aspirated the aqueous humor with a fine syringe, after which we laid the cornea open at its limbus and, with its concavity upward, placed it on the meter chamber. On top of this we placed the aqueous humor, and then determined the permeability of the aqueous humor plus the cornea (fig. 3).

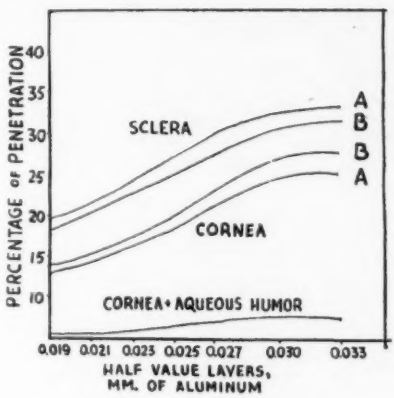

Fig. 2.—Curves showing the percentage of rays passing through the sclera, the cornea and the cornea plus aqueous humor of 2 rabbits (*A* and *B*).

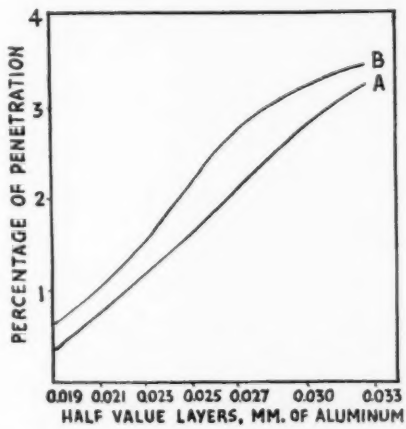

Fig. 3.—Curves showing the percentage of rays passing through the cornea and aqueous humor of 2 rabbits (*A* and *B* of figure 2). These curves are on a larger scale than those in figure 2; otherwise the conditions were similar.

The following experiments were also carried out: The rays were sent through the sclera together with the adhering parts of the conjunctiva, the laterally situated portions of the sclera (which are preponderantly concerned clinically and are different in thickness from other portions) preferably being used.

After these experiments on the organs of rabbits had given consistent results, we proceeded to investigate absorption in the human cornea and sclera. For technical reasons, the aqueous humor could not be aspirated as it was in the rabbit eyes.

We had the opportunity of studying 3 specimens of intact human cornea, obtained after enucleation. Cornea 1 was used four hours after operation; it was not placed in any kind of fixing fluid, but was kept in a moist chamber. Cornea 2 was examined twenty hours after operation under similar conditions. Cornea 3 was kept in Müller's fluid for three days. Since it had to be assumed that this procedure would produce considerable changes in the organ, which would have some bearing on the results, cornea 2 was also placed (after the first experiment) in Müller's fluid for three days, and then another examination was carried out. The differences in the results obtained in this way were, however, insignificant and within the limit of inaccuracy. For example, with a half value layer of 0.019 mm.

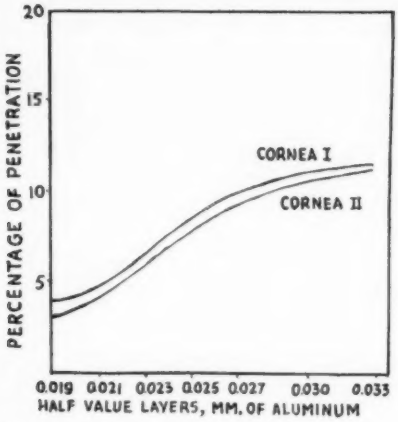

Fig. 4.—Curves showing the percentage of rays passing through 2 human corneas.

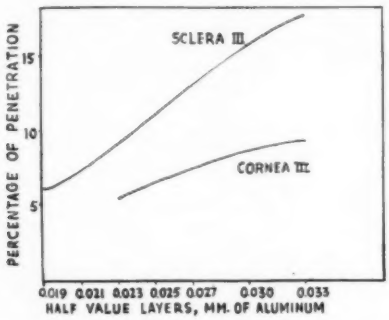

Fig. 5.—Curves showing the proportion of rays passing through a human cornea and a human sclera.

of aluminum, the result was 3.5 per cent at first and after three days 3.3 per cent. With a half value layer of 0.033 mm., it was 11.9 per cent and afterward 11.7 per cent.

If the tissue is kept in solution of formaldehyde for some time, its absorptive qualities are altered to a considerable extent. Through fixation, the rate of absorption is increased at first; after some weeks, however, when the cornea has become thinner, it is considerably reduced.

Figures 4 and 5 contain absorption data for corneas and scleras of human beings.

Before drawing conclusions from the foregoing results one should recall the anatomic structure of the eyeball.

The measurements shown in figure 6 are mean values. Thus, the following picture is presented:

1. If a vertical beam is applied, enough rays are absorbed by the aqueous humor to allow but a small proportion to reach the lens (in the rabbit, 0.65 to 3.45 per cent).

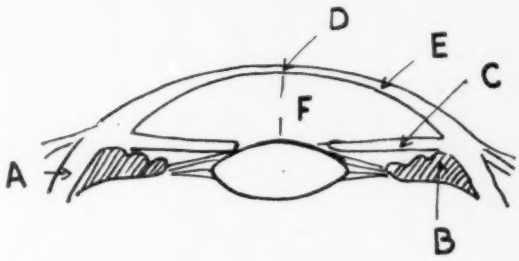

Fig. 6.—Diagram showing the thickness in mean value of various portions of the eye: *A*, sclera at limbus, 0.825 mm.; *B*, ciliary body, thickest portion anteriorly, 0.8 mm.; *C*, iris, maximum, 0.6 mm.; *D*, cornea, center, 0.4 to 0.67 mm.; *E*, cornea 20 degrees from the center 0.8 mm.; *F*, anterior chamber, average, 2.7 mm.

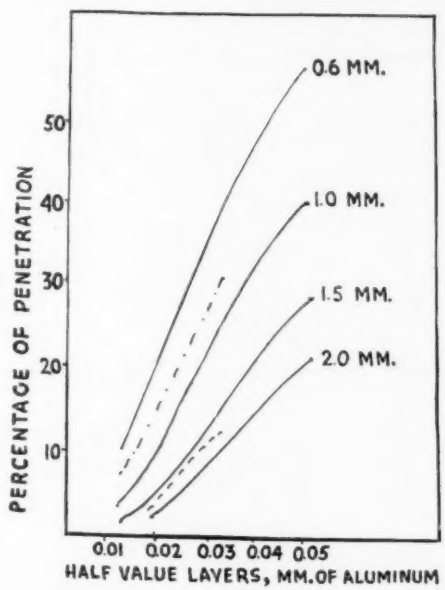

Fig. 7.—Quantity of rays in terms of percentage of the surface dose, as recorded at various depths, for rays with half value layers from 0.01 to 0.05 mm. of aluminum, the thickness of the organs under consideration being 0.6 to 2 mm. The determinations were made on animal tissues. Only part of the curves, which are from Ebbehøj,[17] are given here. The line of dots and dashes represents an 0.8 mm. thickness of skin and the line of dashes an 0.8 mm. thickness of human cornea.

2. If the beam is directed on the limbus or sclera (the average thickness of the sclera being assumed to be 0.825 mm.), the nonabsorbed portion of the rays is 6 to 18 per cent, and a comparatively large percentage of rays reach the ciliary body. Since this organ is of particular significance, being the vascularized part

of the eye, injury to it is of prime importance. On the other hand, it is particularly by way of this organ that the effect desired may be produced.

In its thickest part the ciliary body is roughly 0.8 mm. Assuming, therefore, that another half of the original quantity of rays is absorbed here, 3 to 9 per cent would penetrate the sclera plus the ciliary body.

3. Similarly, in the region of the limbus, the iris receives 6 to 18 per cent of the rays.

A comparison of these results with Ebbehøj's [17] absorption curves for the skin is pertinent. The experiments of this author were conducted on the detached ears of rabbits, mice and calves. The absorption curves obtained, Ebbehøj stated, were similar to those obtained with paraffinized paper (fig. 7).

The shape of the curves depends not only on the half value layers employed but on the types of rays present in the mixtures. Since, however, the type of bulb as

TABLE 2.—*Absorption Data Obtained with Cornea and Sclera* *

Half Value Layer, Mm. of Aluminum	Cornea 1	Cornea 2	Cornea 3	Sclera
0.019	4.2	3.30	....	6.20
0.021	4.8	4.60	....	7.40
0.023	6.5	5.90	5.30	9.00
0.025	8.6	8.09	....	11.00
0.027	10.0	9.50	....	12.70
0.030	10.6	10.40	8.70	15.30
0.033	11.4	11.10	9.50	18.20

* The figures indicate the intensity of permeation in percentage.

TABLE 3.— *Absorption Data on Skin Determined with Paraffinized Paper (from Ebbehøj)* *

Half Value Layer, Mm. of Aluminum	0.554 Mm.	0.739 Mm.	0.924 Mm.
0.019	27.9	18.6	13.4
0.022	30.2	21.3	16.4
0.024	32.6	24.3	18.1
0.026	35.0	27.2	22.0
0.027	39.0	30.4	23.3
0.039	41.6	32.6	24.6
0.034	48.7	38.5	32.6

* Only part of the table is given. The peak kilovoltage was 9 to 14, the milliamperage was 3 and the distance from the focus to the diaphragm was 4 to 15 cm. The figures indicate the intensity of permeation in percentage.

well as the voltage and filtration used by us were similar to those employed by Ebbehøj, certain comparisons are permissible.

The average thickness of the cornea has been determined (at a point 20 degrees from the center) as 0.8 mm. If we entered the values obtained by us for corneal tissue into Ebbehøj's curves (substituting for the missing item 0.8 mm., the mean between 0.6 mm. and 1.0 mm.), we found that with a half value layer of 0.019 mm. of aluminum, the permeability of the skin was between 13.4 and 27.9 per cent, with a mean of about 20 per cent. The figures obtained for the cornea were 3.3 to 4 per cent, which would indicate that 500 per cent more rays permeate the skin than permeate the cornea.

With the hardest variety of the rays (half value layer, 0.033 mm. of aluminum), the permeability of skin 0.8 mm. thick would be more than 30 per cent. The

17. Ebbehøj, E.: Untersuchungen über ultraweiche Röntgenstrahlen, ihre Tiefendosiskurven und das Verhältnis zwischen ihren biologischen Wirkungen, Copenhagen, Nyt Nordisk Forlag, 1937.

cornea would allow only 11 per cent of the rays to pass. It thus appears that with this half value layer, 250 per cent more permeate the skin.

The values between the two half value layers indicated are shown in the accompanying tables and curves.

Comparing our curves with those obtained by Ebbehøj with his model material and animal tissues, we can make the following statements: With the same thickness, the cornea and the sclera show a far greater absorption than the skin, which means that the percentage of rays permeating these layers is smaller than that permeating a piece of skin of the same thickness. Differences of 250 per cent and 500 per cent were recorded between skin and cornea and of 100 per cent between skin and sclera.

In table 2 the values obtained with sclera and cornea are given, and in table 3, those obtained by Ebbehøj with paraffinized paper.

These figures mean that in rabbits (the total dose of Krasso, 750 r, and a direct beam being used) 4 to 25 r reach the lens. In human beings, however, the anterior chamber is considerably deeper, so that only a few roentgens may reach the lens, a quantity which—if an actual therapeutic effect is obtained—should easily be borne. Conditions are different when higher doses are concerned. With a total of 5,000 r, a rabbit (with a direct beam) would receive 25 to 175 r on its lens; if indirect rays were applied by way of the sclera, 150 to 450 r would reach the ciliary body and the iris, and a certain part would reach the lateral portions of the lens via the posterior chamber. Such doses closely approach the limit of what can be applied to the lens without causing damage (this is also true of the blood vessels of the ciliary body), and it cannot be foreseen whether later disturbances will develop, particularly since one is dealing with an organ in which the cumulative absorption is almost 100 per cent.

With the softest variety of the rays (half value layers of 0.019 and 0.021 mm. of aluminum), conditions are very different; the penetration is only about one third of that which occurs with a half value layer of 0.033 mm. of aluminum. One can use much higher doses without damage.

Application of the large doses is justified only when the process in the eye is so serious that the possible development later on of a lesion in the lens must be disregarded. If vision is preserved, subsequent extraction of the lens will restore the function of the eye.

The dose, however, has to be decided in every case separately. To discuss the tolerance to high doses and the biologic reactions which may occur would be to exceed the scope of this paper, in which we have been dealing only with the absorption of rays taking place in certain kinds of tissue.

SUMMARY

Experiments were set up to determine the permeability of the anterior portion of the eyeball to infra-roentgen rays (those for which the half value layers are between 0.019 and 0.033 mm. of aluminum). Data obtained for rabbit cornea, sclera and aqueous humor and for human cornea and sclera are given. These are compared with data for skin.

Therapeutic possibilities are discussed, and attention is drawn to the relative innocuousness of even high doses of these rays.

Rothschild-Hadassah-University Hospital.

ASSOCIATION BETWEEN ANISEIKONIA AND ANOMALOUS BINOCULAR SPACE PERCEPTION

KENNETH N. OGLE, PH.D.
HANOVER, N. H.

Early in the research in aniseikonia, it was recognized that differences in the size and shape of the ocular images of the two eyes have an important effect on correct binocular (stereoscopic) spatial localization. This localization takes place over the entire binocular visual field and is not restricted to the discrimination of differences in depth in the central field of vision. Many of the basic facts concerning the relationship between anomalous binocular spatial localization and the difference in size and shape of the ocular images were brought out in the early studies on the horopter.[1] It was shown that a rotation and a distortion of the longitudinal horopter occur when the relative sizes of the images from the two eyes are changed by "size" lenses placed before the eyes. Corresponding disturbances in binocular spatial localization were shown to take place with less simplified objects, as in the studies on the so-called "tipping boards."[2] More recent studies with such devices as the "leaf room" and the "space eikonometer"[3] have been concerned specifically with the many aspects of incorrect binocular spatial localization associated with the specific types of anomalous ocular image incongruities.

Many experiments with these instruments have demonstrated that persons with normal eyes and good visual acuity experience, with a high sensitivity, the incorrect binocular spatial localizations associated with the various types of ocular image incongruities introduced by size lenses. The spatial distortion caused by image size differences of the order of 0.1 to 0.2 per cent is readily detected. In those tests in which the subject can himself adjust the magnification units or the test elements themselves, mean variations for a given set of data of $\pm$ 0.06 per cent image size difference were not unusual.[4]

Many experiments on different apparatus have shown also that with a given ocular image incongruity the magnitude of the apparent incorrect binocular localization varies with the type of test apparatus and also to a certain extent with the individual subject. This magnitude more nearly approaches the theoretic magnitude called for by the incongruity, the freer the given test is from mononuclear clues to space perception, such as perspective from rectilinear detail and from known forms. Thus in the average room, with the rectilinear detail of floor, baseboards, chair rails, windows, etc., a person might not experience the distortion caused by wearing a size lens before one eye. The same person would experience the distortion on

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From the Research Division of the Dartmouth Eye Institute.

1. Ames, A., Jr.; Ogle, K. N., and Gliddon, G. H.: Corresponding Retinal Points, J. Optic. Soc. America **22**:538 and 575, 1932. Ames, A., Jr.; Gliddon, G. H., and Ogle, K. N.: Size and Shape of Ocular Images: I. Methods of Determination and Physiologic Significance, Arch. Ophth. **7**:576-597 (April) 1932. Ogle, K. N.: Die mathematische Analyse des Längshoropters, Arch. f. d. ges. Physiol. **239**:748-766, 1938.

2. (*a*) Ames, A., Jr.: Aniseikonia: A Factor in the Functioning of Vision, Am. J. Ophth. **18**:1014-1020, 1935. (*b*) Ogle, K. N.: The Induced Size Effect, Arch. Ophth. **20**:604-623 (Oct.) 1938.

3. Complete descriptions of these instruments are to be published by Adelbert Ames Jr.

4. For test elements which subtend a visual angle of 8 degrees, this mean deviation corresponds to a visual angle of about 20 seconds of arc.

a large lawn or in the woods. A person with a highly developed or trained stereoscopic sense might even see the distortion in normal environments.

Early [2a] in this research, the results suggested that the asthenopic symptoms that frequently arise from aniseikonia were due, at least in part, to the nervous conflict that would exist between incorrect binocular (stereoscopic) spatial perception and the perception originating in monocular vision—perspective and known forms.

The question that had not been answered in all these studies, however, was whether persons with aniseikonia, especially those who had had aniseikonia for some time, would show anomalous binocular spatial localization and, if this was found, whether it would be of the nature and amount demanded by the aniseikonia present. The development of the so-called space eikonometer and the leaf room provided the instruments for studying this question. The primary purpose of this paper is to present comparative data obtained with the space eikonometer and the leaf room, which depend in the main for their operation on binocular (stereoscopic) spatial localization, and with the standard eikonometer as now used in clinical practice. The study involved was by nature essentially a statistical one and as such was carried out as a part of a research project in the clinical division of the Dartmouth Eye Institute, where persons having aniseikonia were available.[5]

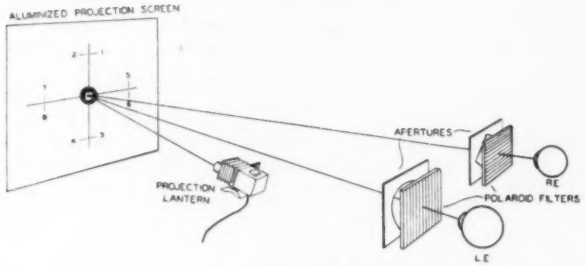

Fig. 1.—Schematic representation of the standard eikonometer.

INSTRUMENTS

The standard eikonometer needs to be described only briefly here.[6] It consists essentially of an eikonic target, a test lens unit before the subject's eyes and a head rest. For the distant vision test, the detail of the eikonic target is projected on an aluminized screen by a lantern (fig. 1). The central pattern of the two dimensional target consists of a vertical and a horizontal line intersecting at a circular configuration, which stimulates and maintains fusion. At an angular distance of 4 degrees from this center, four pairs of numbered opposing arrows are located in the vertical and horizontal meridians. By means of polaroid material, the light coming from the odd-numbered arrows and numbers is polarized in one direction; that from the even-numbered arrows and numbers is polarized in the direction at right angles. Correspondingly oriented polaroid plates are placed before the subject's eyes so that he will see the odd-numbered arrows with one eye and the even-numbered arrows with the other. The central configuration is left unpolarized, to be seen by both eyes. The head rest holds the subject's head so that the eyes will be in a fixed position relative to the test lenses and to the eikonic target.

5. The research of Professor Adelbert Ames Jr. laid the foundation for this project.

6. Madigan, L. F.: Measurement and Correction of Aniseikonia, Hanover, N. H., Dartmouth Eye Institute, 1942. Ames, A., Jr.: Aniseikonia, in Piersol, G. M.; Bortz, E. L., and others: The Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1936, vol. 13, p. 730. Berens, C., and Loutfallah, M.: Aniseikonia, Am. J. Ophth. **22**:625-641, 1939.

Through this test arrangement only a linear comparison of the sizes of the ocular images from the two eyes is possible. All monocular clues for spatial localization as well as the disparities for stereoscopic depth localization are excluded. By asking the subject to compare the apparent distances between opposing arrows as seen by the two eyes, fusion being maintained by the target center, one ascertains the image size differences. If there is no aniseikonia present in the vertical and horizontal meridians, all the pairs of opposing arrows will be seen in alinement.[7] If all even-numbered arrows are seen outside the odd-numbered arrows, image size differences exist in both the vertical and the horizontal meridian.

The magnitude of the image size differences that may be present in a given case is measured by special magnifying lens units[8] before the subject's eyes. These units are adjusted so as to magnify the image in the eye with the smaller image until the subject reports that the odd-numbered and even-numbered opposing arrows are seen in alinement. Magnification so introduced can then be read from scales on the units in percentage magnification. In actual practice the measurement of aniseikonia usually involves the determination of the limits of magnifications introduced by the lens units within which the subject reports equality of the two ocular images. The aniseikonia present is measured to the midpoints of these limits. One-half the range between these limits (expressed ± per cent) is designated the "sensitivity" of the subject to a particular part of the test and may be identified with the subject's precision of measurement. The procedure is to ask for reports from the subject for different adjustments of the magnifying test lenses.

The space eikonometer depends on binocular spatial localization, essentially stereopsis, acting over the entire binocular visual field. As the name would imply, the instrument is for measuring the type and degree of ocular image incongruities by obtaining them from the corresponding false, or anomalous, binocular space perception. The problem of design of such an instrument is to devise the visual test elements, or objects, so that by their apparent positions, or orientations, they can be used separately or in combination to measure each of the several types of ocular image incongruities. It is necessary to eliminate all empiric or monocular clues which would tend to interfere with "pure" binocular stereoscopic spatial localization, that is, with the space perception derived only from disparities of the images of the two eyes. The simplest type of contours are necessary, adequately screened from all other binocularly seen objects and influences of the room.

The particular apparent position of the elements as seen by an observer is affected by differences in size or nature between the ocular images of those test elements in the two eyes. By ascertaining the nature and degree of the incorrect perception of the test elements, one can arrive at the nature of the relationship between the ocular images of the two eyes.

The instrument[9] consists of three parts: a system of test elements, a magnifying lens system before the subject's eyes and a head rest (fig. 2). The test elements used for the present investigation were (*a*) an oblique cross made up of two smooth-stretched cords at right angles to each other and (*b*) two pairs of smooth vertical plumb cords, erected two in front and two behind the cross. The cross, stretched from the corners of a 5 foot (152 cm.) square frame, is set up vertically

7. The measurements are usually complicated by "fixation disparities," which occur when heterophorias are present, in that an equal displacement in the same direction of opposing arrows takes place.

8. Ogle, K. N.: An Optical Unit for Obtaining Variable Magnification in Ophthalmic Use, J. Optic. Soc. America **32**:143-146, 1942.

9. A more complete description of the instrument will be published later.

at a distance of 3 meters from the subject's eyes. The plane of the cross is carefully mounted at right angles to the subject's objective median plane. Two of the vertical plumb cords are suspended 60 cm. in front of the cross and two behind. Separated about 50 cm., they subtend an angle of approximately 12 degrees to the observer. The cords are equidistant from the subject's objective median plane, and each is accurately suspended the same distance from the subject's eyes. Suitable apertures restrict the subject's binocular field of view to the test elements. The test magnification lenses are similar to those on the standard eikonometer. The head rest and chin cup support the subject's head, so that the eyes are in a fixed position relative to the lenses and to the system of test elements.

If a difference exists in the size of the ocular images, or is introduced by size lenses in the horizontal meridian only, one of each pair of the vertical cords will appear nearer to the subject than does the other. Also, the cross will appear rotated about a vertical axis. The nearer cord and the nearer side of the cross will be on the side of the eye having the smaller ocular image. By increasing the size of the image in this eye in the horizontal meridian by means of the magnifying test lenses, one can make the cords appear equidistant from the observer. If a difference in the size of the ocular images exists, or is introduced by size lenses, in

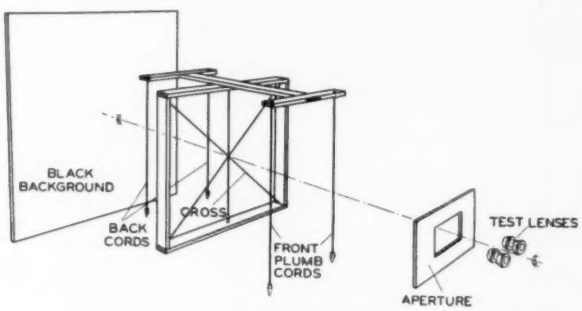

Fig. 2.—Schematic drawing of the space eikonometer, showing the essential parts.

the vertical meridian alone, only the cross will appear rotated, the farther side being on the side of the eye having the smaller image. By magnifying the image in that eye in the vertical meridian by means of the test lenses, one can make the two sides of the cross appear the same distance from the subject. Thus the presence and magnitude of a horizontal and a vertical image size difference can be detected and measured by the difference in the apparent rotation of the vertical plumbs and the cross.[10] The data are obtained, as with the standard eikonometer, by questioning the subject regarding the apparent positions of the test elements when the examiner makes different adjustments in the test lenses, and again a method of limits is applicable. The sensitivity of each subject was taken as one-half the range of magnification of the test lenses within which the subject reported that the test elements appeared normal. Anomalous binocular spatial localization is thus measurable in the vertical and horizontal meridians, in terms of the corresponding ocular image incongruities in those meridians.[11]

10. These apparent rotations can be accounted for wholly by the geometry of the instrument and the stereoscopic depth perception resulting from horizontal disparities.

11. The cross of this instrument will appear to rotate about a horizontal axis when the meridional image size differences are in oblique meridians or when a cyclotorsion of the ocular images is present. This phase of the instrument, not being of concern in the present paper, will not be touched on, but will be considered fully in the near future.

The leaf room might be said to be more truly a "functional" instrument, since its characteristics more nearly conform to normal environments. The room [9] is a rectangular box about 7 feet (215 cm.) square, open at one end, with the walls vertical and the floor and ceiling level. The subject views the room from the center of the open end, with the head held in position by a chin cup (fig. 3). To the inside surfaces (painted black) are stapled artificial vines with the leaves individually adjusted so that they stand out uniformly from the surface. The rough surfaces of the leaves when properly illuminated provide many contours to stimulate binocular stereoscopic vision and yet introduce only a minimum of monocular clues to perspective, which might tend to inhibit the binocular perception. On the other hand, the corners of the room outline a definite cubic shape, which, though introducing a slight degree of rectilinear perspective, does make for an easy description of the visual experience of an observer.

The nature of the binocular spatial localization is determined from the subject's description of the apparent positions, shapes and sizes of the walls, ceiling and floor and of the leaves themselves as he looks into the room. Definite patterns of dis-

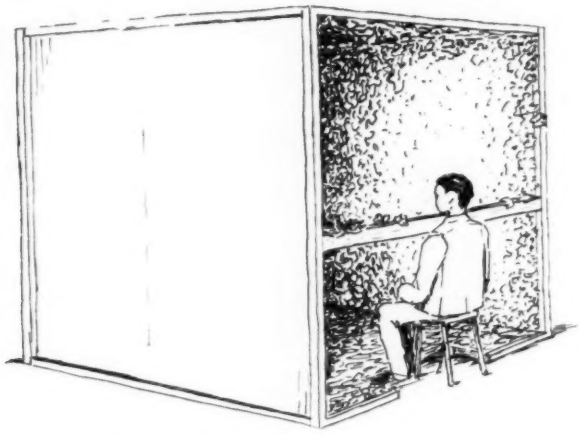

Fig. 3.—Schematic drawing of the leaf room.

tortion of the room are associated with the particular types of regular ocular image incongruities present. The examiner thoroughly familiar with these distortions will readily recognize the distortion associated with a particular type of image size difference. Since the distortions affect the whole room, various parts of the room may be used to check others in a given pattern.

The test in the leaf room is a valuable adjunct to the space eikonometer but cannot easily be used alone to determine the exact nature of the ocular image incongruity causing the distortion. It is usually difficult to separate the distortion due to an image size difference in the horizontal meridian from one due to a difference in the vertical meridian.[12] Moreover, little or no distortion appears from an over-all image size difference. Because of these facts, the examiner is forced to rely on the space eikonometer for differentiation of the meridional image size differences and on its measurement of over-all differences.

12. The leaf room is especially valuable in revealing several other types of ocular image incongruities, but since these are not pertinent to this study, they will not be described in this paper.

Persons with normal binocular (stereoscopic) spatial localization see the leaf room in its true rectilinear form; those with anomalous ocular incongruities usually see it distorted. However, the fact that an observer reports the appearance of the leaf room as being in its true form is not proof that there are no anomalous ocular image incongruities present. He may be relying on uniocular visual clues for his spatial localization and even in the simplified environment of the leaf room may be suppressing the binocular clues.[13] The test in this case is to determine the subject's response to the effect of artificial image size differences as introduced by various types of size lenses. The normal person will perceive similar abnormal appearances of the room, in opposite directions, when meridional size lenses that produce small image size differences (0.2 to 0.5 per cent) are placed before one eye and then the other. A subject with aniseikonia, however, will respond differently. With such a person to produce a corresponding amount of distortion of the room in opposite directions, it is necessary to use a meridional size lens that introduces a larger image size difference before one eye than before the other. Thus the technic of testing the correctness of a subject's binocular spatial localization in the leaf room is to determine his response to a systematic series of size lenses of low magnification and to determine the symmetry of response.

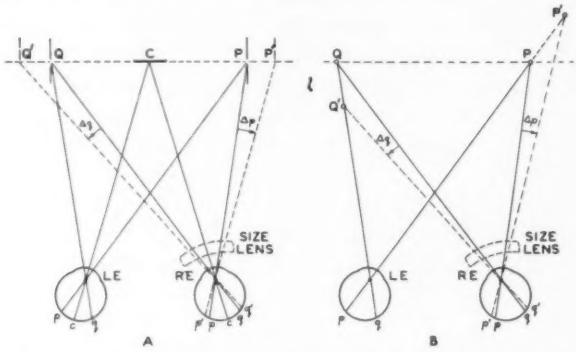

Fig. 4.—Schematic representation of the elements on which depend the standard eikonometer, the space eikonometer and the leaf room. *A*, standard eikonometer. *B*, space eikonometer and leaf room.

The procedure is, therefore, to place the size lenses corresponding to the correction found on the space eikonometer in a trial frame and place this before the subject's eyes. The subject is then seated before the leaf room, and the examiner ascertains the nature of any anomalous appearances present by questioning. Care is exercised, of course, to avoid leading questions. The check on the subject's answer is to insert a meridional size lens of low percentage magnification before one eye and then the other, in the horizontal meridian and then in the vertical meridian. In each case the subject's answers are noted. If he fails to experience the anomalous appearance that should be caused by the given lens, size lenses of increasingly higher magnification are used until the correct distortion is perceived. The range of magnifications used within which no distortion is seen is again related to the sensitivity of the patient to this particular incongruity. The image size difference is taken to the midpoint of this range and added to the space eikonometer finding for the final result. A check is also made on the distortion of the room without size

13. There may be a considerable time lag also before the distortion becomes apparent. Frequently a subject first sees the room undistorted, but at the end of a test in which various size lenses have been used he will see a distortion normally.

lenses. While it may be said that the leaf room test is not entirely independent, following the foregoing routine one checks the correctness of a given measurement by it and does so in terms of the sensitivity of the subject to incorrect binocular spatial localization.

The essential differences between these tests will be clear from a study of figure 4. Let P and Q be two points in a frontoparallel plane being observed by the two eyes. The images of P and Q will fall at points p and q on the retinas of the two eyes. If the size of the image of the right eye is now increased (here indicated by a size lens) in the horizontal meridian, the images of P and Q on the retina of the right eye will be displaced to points p' and q', respectively.

With the standard eikonometer (fig. 4*A*), where there is a central configuration at C sufficient to maintain fusion during coordinated ocular movements and where the images of P and Q as seen by the two eyes are disassociated (by polaroid material), the test depends on the subject's uniocular discrimination of the difference in the visual angles, i. e., Δp and Δq, corresponding to the retinal distances pp' and qq'. This discrimination depends, therefore, on the elemental function of the retina, the uniocular sense of relative visual directions.

In the space eikonometer, as in the leaf room, where the images of P and Q are not dissociated (fig. 4*B*), the points P and Q will be seen in stereoscopic relief at positions P' and Q'. Thus, these tests depend on the subject's discrimination of the stereoscopic difference in the apparent distance of P relative to Q, which in turn is determined by the same disparity angles, Δp and Δq. The space eikonometer and the leaf room might be referred to as "functional" testing instruments, since they measure the functional aspect of binocular vision, that is, binocular spatial localization.

Summing up the difference between the three tests, one may say that the standard eikonometer inherently excludes all clues to stereoscopic depth perception and permits an observer to relate linearly two uniocularly seen test patterns with each other; that the space eikonometer excludes all uniocular depth clues, does not necessitate exact positioning of eyes and uses pure binocular depth perception, and that the leaf room differs from the space eikonometer in that it adds to practically pure stereoscopic depth perception a few monocular clues, which, while not strongly impeding the effect of the binocular clues, provide clues to form that disclose the characteristics of the binocular spatial localization.

PROCEDURES

The subjects tested by means of the space eikonometer and leaf room for this study were regular patients for whom image size differences had been measured in the routine clinical test with the standard eikonometer and who were otherwise suitable for the two tests. A number of persons not definitely aniseikonic were, however, also tested. A summary of the results of the examination with the standard eikonometer was sent with each subject referred for the tests. As a precautionary step to keep the two examinations entirely independent, the actual notation of the image size differences measured was sealed, to be opened only at the end of the test with the space eikonometer. Care was taken, especially, that the subject wore in each comparative test properly adjusted spectacles of exactly the same refractive correction.

The image size differences are expressed in terms of the percentage magnifications needed for a given eye to correct those differences. Thus "right 1 per cent, axis 90 degrees" means that in order to correct the image size difference, the image of the right eye must be increased by 1 per cent in the horizontal meridian (axis 90 degrees).

RESULTS

It had long been recognized at the institute that certain persons with aniseikonia showed an anomalous spatial localization such as would be expected from their aniseikonia measured with the space eikonometer and the leaf room. Early in this project it became clear that most persons with an aniseikonic error did, in fact, show an anomalous binocular spatial localization corresponding to the error shown by both the space eikonometer and the leaf room. The problem then became one of ascertaining to what extent the aniseikonia measured by means of the faulty binocular spatial localization agreed with that to be expected from the type and amount of aniseikonia present as measured with the standard clinical eikonometer. By measuring the incorrect binocular spatial localization in terms of image size difference or the size lens magnification necessary to correct it, one has an exact method of comparison with the results from the clinical instrument.

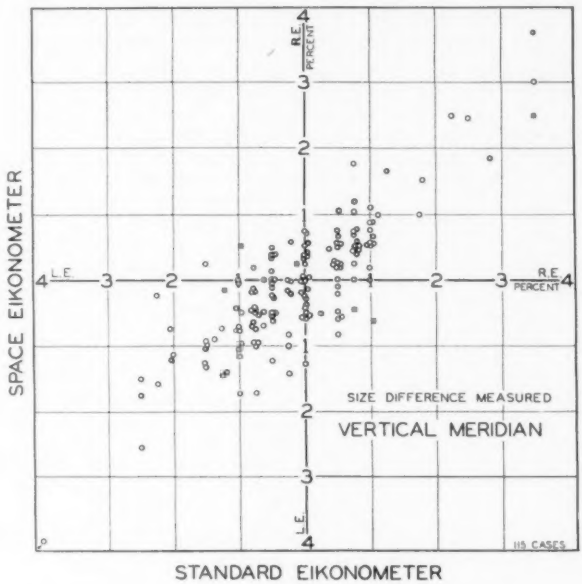

Fig. 5.—Scatter representation of data obtained from measurements on the standard eikonometer and on the space eikonometer.

The data on 156 patients referred to the aniseikonia clinic for examination were available for comparison. These patients represent all those subjects who were tested completely by means of the three instruments and with whom the tests were made under the same refractive conditions. Of these subjects, 35 were classified by the clinicians as being either nonaniseikonic or on the borderline of aniseikonia on the basis of measurements and symptoms.

A. *Correlation of Aniseikonia Measured on Standard Eikonometer with That Measured by Anomalous Binocular Space Perception on Space Eikonometer.*—Figures 5 and 6 are the scatter diagrams of the data for the standard eikonometer and the space eikonometer, showing the distribution of the subjects for the vertical and for the horizontal meridian, respectively. The position of each point indicates the image size measurements from the two tests, those from the standard eikonometer being plotted on the abscissa and those from the space eikonometer being plotted on the ordinate. The more nearly all the points in these diagrams fall on

a straight line, the higher the linear correlation will be between the measurements from the two instruments. A perfect correlation could be expected only for mathematically related quantities. However, even a casual inspection of these charts shows clearly that a good correlation does exist, since the points tend to cluster about a 45 degree line through each graph.

Statistical treatment of all the data shows that the measurements are correlated by 0.86 and 0.82 (Pearson's correlation coefficients), with standard errors of 0.05 and 0.06 for the vertical and for the horizontal meridian, respectively. These correlations are highly significant, being generally higher than those usually found between physiologic and the corresponding functional data. The analysis shows also that 68 per cent of the measurements from the two instruments agree within 0.5 per cent and 0.6 per cent for the two meridians, respectively. Moreover, if all measurements which are less than the sensitivity (the precision of measurement) are eliminated from this analysis, the correlations become somewhat higher (0.97

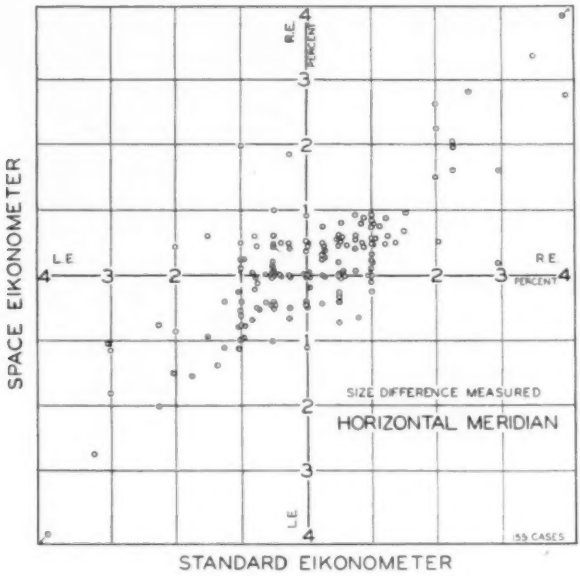

Fig. 6.—Scatter representation of data obtained from measurements on the standard eikonometer and on the space eikonometer.

and 0.90, respectively). The average ratio of the finding from the space eikonometer to that from the standard eikonometer appears slightly less than unity; thus there is some indication that the measurement from the space eikonometer may be 10 to 20 per cent lower than that from the standard eikonometer. However, when the data of the space eikonometer are weighed for these ratios, their distribution is only slightly affected; hence it is concluded that the difference between the instruments is not a consistent one but probably varies with the subject.

Since there was so nearly a 1:1 ratio between the results from the two instruments, the correlation between them may also be studied from the distribution of the subjects according to the differences between the findings. The accompanying table shows the distributions for the vertical and horizontal meridians. An inspection of this table shows again that roughly two thirds of the subjects' data agree within about 0.5 per cent image size difference, the measurements in the horizontal meridian having slightly poorer agreement.

B. *Leaf Room and Space Eikonometer.*—As pointed out in the description of the instruments, the leaf room cannot easily be used alone to determine the exact nature of the ocular image incongruity causing an anomalous appearance of the room. The room is a valuable adjunct, however, for checking the findings of either the space eikonometer or the standard eikonometer, and in that capacity it was used in this project. By the method described, in which different size lenses are used before one eye or the other, one can ascertain the extent to which a given correction as found on the space eikonometer must be modified to make the leaf room appeear rectilinear.[14] Even this modification may be equivocal, and the operator will have to look for suggestions elsewhere in the data, such as in the sensitivities, to determine the exact nature of the modification. However, this procedure has been found to provide a basis for correlating the findings from the leaf room with those from the space eikonometer.

The correlations between the data from the space eikonometer with those from the modified findings from the leaf room are high (correlation coefficients of 0.83 and 0.84 for the vertical and for the horizontal meridian, respectively.) These high correlations emphasize the importance of the correlations between the space

Tabulation of the Number of Subjects Whose Image Size Difference Measured on the Standard Eikonometer and on the Space Eikonometer Agreed Within Specified Differences (156 Subjects)

Difference Between Measurements from the Two Instruments, Percentage	Vertical Meridian			Horizontal Meridian		
	Number of Subjects	Percentage of Subjects	Cumulative Percentage	Number of Subjects	Percentage of Subjects	Cumulative Percentage
0 -0.25, inclusive	67	43	43	64	41	41
0.25-0.50	40	26	69	34	22	63
0.50-0.75	25	16	85	19	12	75
0.75-1	13	8	93	15	10	85
1 -1.25	5	3	96	10	6	91
1.25-1.50	4	2	98	6	4	95
1.50-1.75	1	1	99	1	1	96
Over 1.75	1	1	100	7	4	100

eikonometer and the standard eikonometer, which show that aniseikonic patients as they are tested in the clinic have an anomalous binocular space sense that is manifest in environments where there are few uniocular visual clues.

C. *Repeatability.*—These results become even more significant when they are considered from the point of view of the repeatability of the data obtained with each instrument.

The study of the repeatability of the measurements on the standard eikonometer[15] showed that better repeatability than 0.5 per cent could not really be expected; yet in the vertical meridian in 90 per cent of the cases and in the horizontal meridian in 86 per cent the repeat measurement checked roughly within 0.5 per cent. The correlation coefficients (Pearson) for the tests were 0.87 and 0.76 for the two meridians, respectively.

Repeatability data for the space eikonometer are available for only about 25 subjects. The repeat test was made on an average of about one month after the original test. The data indicate that repeatability for the space eikonometer is

14. Again, this usually involves consideration of other ocular image incongruities, besides the horizontal and vertical differences, but these will not be considered here.

15. Ogle, K. N., and others: Repeatability of Ophthalmoeikonometer Measurements, Arch. Ophth. **24**:1179-1189 (Dec.) 1940.

somewhat higher than that for the other instrument (correlation coefficients 0.95 and 0.94 for the two meridians). Data for 4 members of the staff, taken from time to time during the project, showed average deviations from the means of the series of ± 0.14 and ± 0.20 per cent image size difference for the vertical and for the horizontal meridian, respectively. The average maximum deviations from the means of the series were about two and one-half times these mean deviations.

The repeatability of the data for the leaf room was of the same order as that for the space eikonometer.

CONCLUSIONS

The results of this study are important from three points of view:

1. The data present evidence demonstrating that the subject with ocular image incongruities (aniseikonia) is subject to an anomalous binocular (stereoscopic) spatial localization which, while not apparent in ordinary surroundings, becomes manifest as soon as the field of vision is restricted to an environment where there are few strong clues from perspective or known form. The subjects of the project were routine aniseikonic patients, many of whom had had aniseikonic symptoms of long standing. The results of the project would indicate, further, that when a patient is given iseikonic lenses to correct measured size differences, the anomalous binocular spatial localization is also corrected. The presumption can be made that the person with uncorrected aniseikonic errors must be subject to the stimuli for a false binocular spatial localization even though this anomalous localization is apparent only in environments which have few uniocular clues to space perception.

2. Image size differences can be detected and measured by means of instruments that depend on binocular (stereoscopic) spatial localization. The perfect instrument probably has not yet been invented, but it is believed that the space eikonometer points the way to such an instrument.

3. The data from this project, it is believed, definitely clear up the aniseikonia-anisophoria problem.[16] It has been suggested that because the measurements on the standard clinical eikonometer involve ocular movements on the part of the subject as he looks from the central part of the target to the dissociated test lines (fig. 1), the measurement for aniseikonia may in fact be a determination of anisophoria or of the difference in prismatic deviation caused by anisometropic corrective lenses. This suggestion has been made on the premise that the central configuration at the eikonic target is insufficient to maintain fusion during the coordinated ocular movements. In spite of the experiments which show that the innervations from peripherally seen objects are strong enough to control fusion movements,[17] comparative data on aniseikonia and anisophoria have been lacking.

The high correlations between the standard eikonometer and the two "functional" instruments show definitely that, in general, the measurements on the standard eikonometer must be measurements of image size differences.[18] The incorrect binocular spatial localization can be accounted for only in terms of differences in size and shape of the ocular images of the two eyes and not in terms of phoria and its variations or in terms of differential movements of the eyes necessary to maintain fusion.

Dartmouth Eye Institute.

16. Friedenwald, J. S.: Diagnosis and Treatment of Anisophoria, Arch. Ophth. **15**:283-307 (Feb.) 1936.

17. Burian, H. M.: Fusional Movements: Role of Peripheral Retinal Stimuli, Arch. Ophth. **21**:486-491 (March) 1939.

18. This statement must not be taken to imply that under certain circumstances heterophorias do not affect the use of the standard eikonometer, for they frequently do, especially at near vision.

LOCAL TOXIC EFFECTS OF SULFANILAMIDE AND SOME OF ITS DERIVATIVES

JOHN G. BELLOWS, PH.D., M.D.
WITH THE LABORATORY ASSISTANCE OF ROBERT GLUCKMAN, B.S.
CHICAGO

Since the topical application of the sulfonamide compounds is gaining widespread use in many branches of surgery, it is imperative that knowledge of the local tissue reaction to these drugs, which is meager and of controversial nature, be increased. The chemotherapeutic effectiveness of the drugs is too well established to require either discussion or review of the literature in this report.

The in vitro studies of Jacoby and associates [1] revealed that sulfanilamide, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) produce unfavorable morphologic effects and inhibition of growth in living fibroblasts, macrophages and epithelial cells. These authors found that in equal concentrations sulfathiazole is the most toxic, but stated that under clinical conditions the toxicity depends on the solubility of the drugs. They are soluble in descending order as follows: sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine. Bellows and Chinn [2] found that a moderate reaction, indicated by chemosis and epithelial staining, occurs when sulfanilamide powder is applied to the cornea. Hawking [3] and later Chambers and associates [4] found that sulfanilamide causes a slight depression in the formation of fibroblasts. The necrotizing action of the sodium salts on the epithelium of the nasal accessory sinuses reported by Fletcher [5] and Futch and associates [6] is attributable to the high alkalinity of such preparations and therefore is not the same type of injury as that caused by the amphoteric form of the drugs under consideration in this report.

Key and Burford [7] were among the first to suggest that the drugs applied locally have a retarding influence on the healing of wounds. This observation was confirmed by Bick,[8] who demonstrated that the local application of sulfonamide compounds to cleancut wounds produces a 50 per cent prolongation in the healing time and results in excessive cutaneous scarring. Further support for these views is found in the reports by Sutton,[9] Ochsner,[10] Reichert [11] and others. Implantation

Dr. Bellows is a recipient of a grant from the Snyder Ophthalmic Foundation.

From the Department of Ophthalmology, Northwestern University Medical School.

1. Jacoby, F.; Medawar, P. B., and Willmer, E. N.: Brit. M. J. **2**:149, 1941.
2. Bellows, J., and Chinn, H.: Distribution of Sulfanilamide in Eye, J. A. M. A. **112**:2023 (May 20) 1939.
3. Hawking, F.: Lancet **1**:786, 1940.
4. Chambers, L. A.; Harris, T. N.; Schumann, F., and Ferguson, L. K.: Use of Microcrystals of Sulfathiazole in Surgery, J. A. M. A. **119**:324 (May 23) 1942.
5. Fletcher, R.: The Caustic Action of Sodium Sulfathiazole, J. A. M A. **117**:1204 (Oct. 4) 1941.
6. Futch, C. E.; Rosenvold, L. K., and Stewart, C. E., Jr.: Caustic Effect of Sodium Sulfathiazole Solution on Nasal Mucous Membranes, J. A. M. A. **119**:7 (May 2) 1942.
7. Key, J. A., and Burford, T. H.: South. M. J. **33**:449, 1940.
8. Bick, E. M.: Observations on Topical Use of Sulfonamide Derivatives, J. A. M. A. **118**:511 (Feb. 14) 1942.
9. Sutton, H. B.: Intraperitoneal Use of Sulfathiazole, with Special Reference to Production of Adhesions, J. A. M. A. **119**:559 (June 13) 1942.
10. Ochsner, A., in discussion on Jackson and Coller,[15] p. 199.
11. Reichert, F. L., in discussion on Jackson and Coller,[15] p. 199.

of sulfathiazole into the peritoneal cavity, wrote Sutton, may lead to severe adhesions. Ochsner stated that sulfanilamide in wounds causes an intense reaction, which leads to excessive exudation and prolonged healing, and that, consequently, the local use of sulfanilamide should be restricted to grossly contaminated wounds. Reichert reported the observations of Laird and Stavern, who found that sulfanilamide when applied to the peritoneum of the normal dog produces no reaction but when applied to the abdominal wall does produce a reaction. This difference between the effects of the sulfonamide compounds on a smoothly lined surface and their effects on a raw surface has been confirmed by us, and its significance is discussed later.

An opposing group of investigators have asserted that the application of the drugs to the tissues not only is innocuous but is actually beneficial. Mueller and Thompson [12] found that the local application of the sulfonamide compounds to the abdominal wall hastens rather than retards the rate of healing of the wound, and consequently they recommended that when "the peritoneal infection is not severe enough to justify the use of sulfanilamide in the peritoneal cavity . . . it is good practice to use 2 to 4 Gm. in the layers of the wall only." The investigations of Taffel and Harvey [13] and Harbison and Key [14] revealed that the tensile strength of wounds is not appreciably affected by the sulfonamide compounds, and Jackson and Coller [15] stated that sulfanilamide actually prevents scarring.

In our investigation of the effects of the local application of the sulfanilamide drugs on the eyeball, we were impressed with the advantages of the cornea as a medium for conduction experiments to provide additional information on the local tissue effects of the drugs. The cornea is particularly suitable for such investigations because it is accessible and transparent and stains in vitro with fluorescein, factors which facilitate the observation of epithelial regeneration. Another advantage is that the second eye offers an ideal form of control.

EXPERIMENTS

The corneas of young adult rabbits were anesthetized by means of a 4 per cent cocaine hydrochloride solution, which was chosen not only for its anesthetic properties but for its drying effect on the epithelium. The drying effect was desired because it facilitated removal of the epithelium, an operation which was accomplished by immobilization of the eyeball with a fixation forceps and rubbing of the cornea with dry gauze.

The cornea was stained with fluorescein to make certain that the epithelium was completely removed. Sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine were used in the form of powder, a 5 per cent ointment and a 20 per cent suspension.[16] The drug to be tested was applied three times daily to one eye, while the other eye served as a control. Through the use of fluorescein we could follow with great precision the epithelial regeneration.

The reactions produced locally by sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine, whether in the form of powder, ointment or suspension, were so nearly alike that the number of animals employed was inadequate for the demon-

12. Mueller, R. S., and Thompson, J. E.: Local Use of Sulfanilamide in Treatment of Peritoneal Infections, J. A. M. A. **118**:189 (Jan. 17) 1942.

13. Taffel, M., and Harvey, S. C.: Proc. Soc. Exper. Biol. & Med. **47**:202, 1941.

14. Harbison, S. P., and Key, J. A.: Local Implantation of Sulfanilamide and Its Derivatives in Wounds, Arch. Surg. **44**:22 (Jan.) 1942.

15. Jackson, H. C., and Coller, F. A.: Use of Sulfanilamide in Peritoneum, J. A. M. A. **118**:194 (Jan. 17) 1942.

16. The drugs were supplied by the Abbott Laboratories.

stration of any notable differences in the effects of these drugs. For this reason, the sulfonamide compounds are considered as a group, and not individually, in this report.

During the first twenty-four hours the treated and untreated eyes showed a moderate generalized injection of the conjunctiva, a haziness of the cornea and the presence of secretion. At the end of twenty-four hours a return of corneal luster and a failure of staining in the periphery of both corneas was the first indication of epithelial regeneration. After this interval, the amount of reaction, determined by the degree of injection and the amount of secretion, decreased in the untreated eye and persisted or even increased in the treated eye. The epithelial regeneration was rapid and continued uninterruptedly on the control side, with the result that in two days 5 of 22 (23 per cent), in four days 11 of 22 (50 per cent), in seven days 18 out of 22 (82 per cent) and in ten days all of the corneas were completely covered with epithelium, the average number of days thus being five and one-tenth. Aside from 2 corneas in which infection was obviously the cause, the untreated corneas recovered, without scars or opacities, in the length of time shown in the accompanying table.

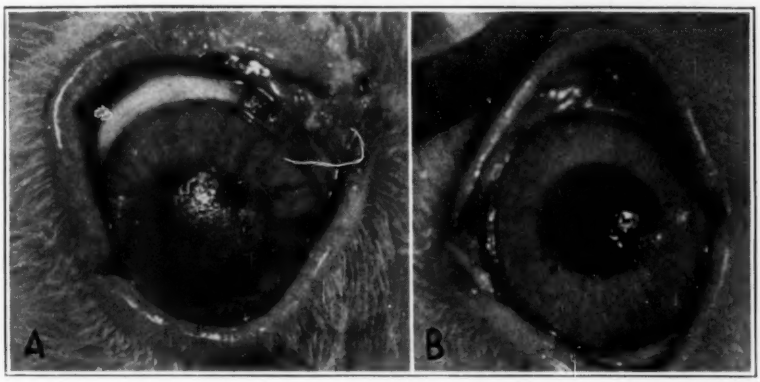

Fig. 1.—Effect of sulfanilamide. *A*, treated eye. *B*, control eye.

Time Required for Regeneration of Corneal Epithelium

Number of days.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Average
Number of control corneas..	..	5	3	3	2	4	1	..	..	4	..	..	..	..	..	..	..	..	..	..	5.1
Number of treated corneas..	..	..	..	..	..	..	..	..	3	3	2	1	4	1	..	5	..	2	..	1	13.3

In contrast to the control group, the eyes treated with sulfonamide drugs healed more slowly, so that in no instance was the cornea completely covered with epithelium before the ninth day. Complete epithelization by the ninth day occurred in only 3 of 22 eyes (14 per cent). Recovery in 13 of 22 of the corneas (59 per cent) was complete by the thirteenth day, and recovery was complete in all the corneas by the twentieth day. Thirteen and three-tenths was the average number of days required for the treated eyes to recover. If anything, these figures are low, because the time of healing would have been greater had it not been that in some instances the application of the drug was stopped at the time of complete recovery of the control eye. In other instances the epithelial regeneration of the cornea did not progress beyond a few millimeters in the periphery until the cessation of use of the drug.

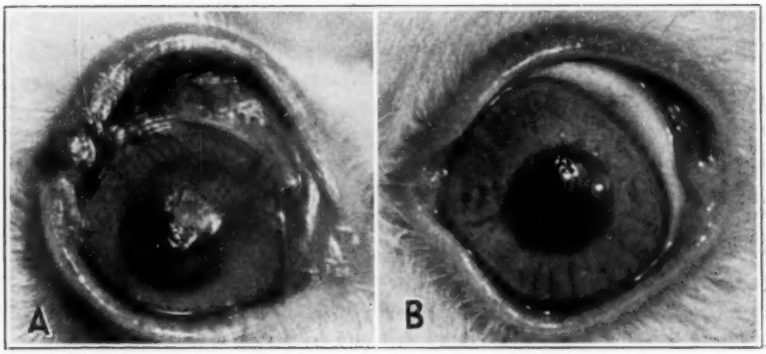

Fig. 2.—Effect of sulfathiazole. *A*, treated eye. *B*, control eye.

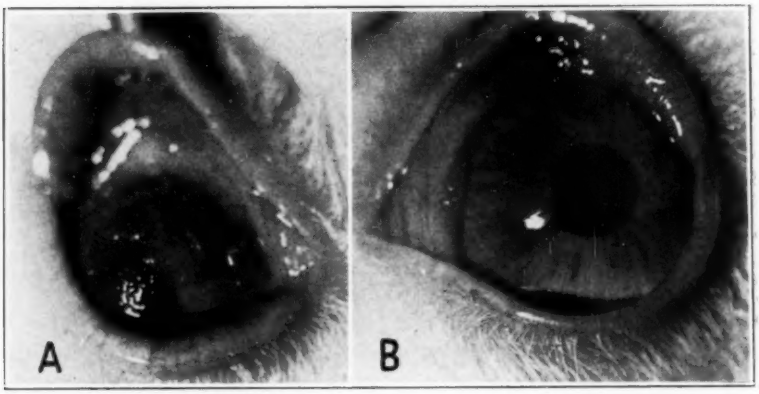

Fig. 3.—Effect of sulfapyridine. *A*, treated eye. *B*, control eye.

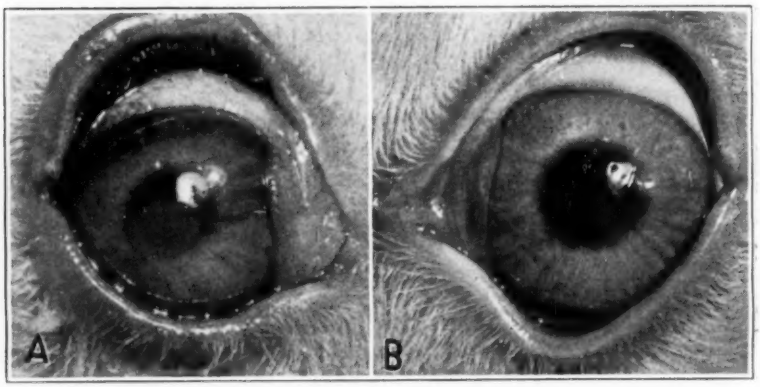

Fig. 4.—Effect of sulfadiazine. *A*, treated eye. *B*, control eye.

The sulfonamide compounds not only caused a delay in epithelization but produced another unfavorable effect, namely scarring, which was found in all the corneas. The scars were macular or leukomatous or a combination of the two. They ranged in size from a few millimeters to almost the entire corneal area. The opacities in some places were raised, with an uneven surface resembling ground glass. Newly formed vessels were invariably present. The vascularization appeared either in the form of large peripheral vessels, which divided into a fine capillary network centrally, or in the form of a pannus, which accompanied the epithelium as it progressed toward the center (figs. 1, 2, 3 and 4). In the slightly scarred corneas the vascularization was more difficult to see but was readily detectable under the proper illumination and magnification.

Microscopic examination of a treated cornea revealed a change consisting either in a loss of identity or complete absence of the basal epithelial layer of the cornea. Noteworthy changes in the deeper layers were absent.

COMMENT

This investigation, in which the rabbit's cornea was employed for the study of local tissue effects of the sulfonamide compounds, yielded additional support of the contention that these drugs prolong the healing time of wounds and promote the formation of scars.

The local toxic action of these drugs has received little experimental attention. The growth of epithelial cells is retarded by the sulfonamide compounds, as is the growth of fibroblasts, as shown by Hawking, Chambers and others. The greater susceptibility of young cells to the toxic action of the drugs may be the explanation for the difference in effect on a smoothly lined surface, such as the normal cornea and peritoneum, with its mature cells, and that on a raw surface, with actively proliferating cells. This difference is of practical importance, for the drugs may be used without fear of local toxic effects on the former type of surface but should be used selectively on a raw surface. For example, when a minimal amount of scarring is desirable, as is the case with lacerations of the face, the local use of the drugs should be avoided unless the danger of infection outweighs this factor. Particular caution is necessary when the corneal epithelium has been denuded by physical or chemical injury, the sulfonamide compounds being avoided except when the injury is such that marked scarring is inevitable. This consideration is especially important in view of the expected increase in such injuries because of the war.

CONCLUSIONS

The sulfonamide compounds have an unfavorable effect on actively growing epithelium, as shown by a greater than twofold increase in the time required for epithelial regeneration. They increase the amount of scarring. Therefore the local use of these drugs should be avoided in the treatment of injuries of the face or cornea.

720 North Michigan Boulevard.

PHYSIOLOGY OF AQUEOUS IN COMPLETELY IRIDECTOMIZED EYES

HAROLD G. SCHEIE, M.D.

ELINOR MOORE, PH.D.

AND

FRANCIS H. ADLER, M.D.

PHILADELPHIA

It has been established that the aqueous humor contains less urea than the circulating blood. Urea should be present in equal amounts in aqueous and blood if the aqueous is formed by dialysis alone, since urea is a crystalloid and a non-electrolyte. It is, however, possible that after the aqueous is formed other processes alter its chemical composition so that it can no longer be recognized as a dialysate. In an attempt to explain this discrepancy a number of factors were explored and reported in a previous paper.[1]

As a result of those studies the low urea content of aqueous was attributed to a lack of permeability of the blood-aqueous barrier to urea. Under normal conditions the membrane separating aqueous from blood does not allow urea to pass through it readily, so that the concentration is always about 20 per cent less in aqueous than in blood. This is true even if the urea content of the blood is artificially elevated and maintained at a new high level. After a considerable period, i. e. about six hours, the level of urea in the aqueous comes into equilibrium with the raised level in the blood, but it is always about 20 per cent less, just as it is in the normal animal with a normal blood urea content (see graph).

The aqueous urea equals the blood urea only under one condition as far as we have found, and that is after the anterior chamber has been opened, the aqueous evacuated and the secondary, or plasmoid, aqueous allowed to form. Under this condition the newly formed aqueous attains a urea level equal to that of blood but holds it for a very short period. Within an hour the urea content of the plasmoid aqueous has fallen to its normal level. No evidence could be obtained of any nervous mechanism controlling the blood-aqueous barrier as far as urea was concerned.

Kronfeld and later Friedenwald and Pierce [2] showed that crystalloids injected into the anterior chamber were absorbed from the aqueous by the iris. The rate of absorption was proportional to the concentration of the crystalloid and depended directly on the area of the iris present. Hence they stated that the iris may be looked on as a simple inert semipermeable membrane separating aqueous from blood. Since the iris itself might play a role in the absorption of urea from the anterior chamber, or for that matter in the formation of aqueous itself, it seemed advisable to devise some means of extirpating the iris from a series of eyes in order to

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From the Department of Ophthalmology, University of Pennsylvania School of Medicine.

Read at the Seventy-Eighth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 2, 1942.

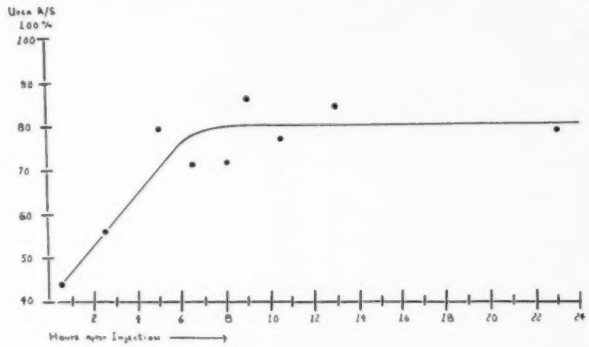
1. Moore, E.; Scheie, H. G., and Adler, F. H.: Chemical Equilibrium Between Blood and Aqueous Humor, Arch. Ophth. **27**:317 (Feb.) 1942.

2. Friedenwald, J. S., and Pierce, H. F.: Circulation of the Aqueous: Reabsorption of Crystalloids, Arch. Ophth. **10**:449 (Oct.) 1933.

evaluate its effect. Friedenwald [3] has pointed out that surgical removal of the entire iris in laboratory animals would be of real experimental value but that up to now this has been accompanied by such severe damage as to leave the eyes unfit for further experimentation. When attempts were made to remove the iris completely from a cat's eye the result was always disastrous; the eye never recovered from the operative insult due to trauma, infection and the persistence of blood in the anterior chamber. Experiments on such an eye are naturally valueless as far as any deductions as to normal function are concerned.

After considerable experimentation and many failures, one of us (H. G. S.) was able to perfect an operation for the complete surgical removal of the iris on a series of cats with a fairly good percentage of successes. Forty-one cats were operated on, and the operation on 44 per cent was successful. The answer to the problem was found to lie in the following factors:

1. Use of a two or three stage operation. A keratome incision was made, and approximately one third of the iris was torn from its base by means of a small biting forceps introduced through the incision. The sector so freed from its base was then excised by radial snips of fine, blunt-pointed scissors. A second and



Equilibration of the urea in the aqueous with that of the blood when the blood urea level is maintained at a new high level.

third operation were then performed as soon as the eye had sufficiently recovered, which was usually within two to three weeks.

2. Avoidance of infection. The first cats of the series were given doses of the sulfonamide compounds by stomach tube or intravenously for several days prior to operation, and at the time of operation these compounds were used locally in the conjunctival cul de sac or introduced into the anterior chamber itself. Later this procedure was found to be nonessential and was dispensed with. Healthy animals were selected and were kept in large separate cages and fed canned salmon and milk or a canned cat food and milk. Maintenance of general health contributes to the success of any operative procedure on cats, which are particularly susceptible to pyogenic infections. The same details for asepsis were observed as in the hospital operating room.

3. Removal of blood from the anterior chamber. It was found that blood remaining in the anterior chamber was a cause for failure in many of the eyes. Blood in the anterior chamber is fairly rapidly absorbed when the iris is present, but if the iris is removed, the absorption of this blood is either considerably delayed or prevented altogether. As a result the eye shows blood staining of the cornea

3. Friedenwald, J. S.: Perspectives in Glaucoma Research, Arch. Ophth. **24**:107 (July) 1940.

and chronic cyclitis and finally becomes phthisical. Since it was not possible to prevent some hemorrhage at operation, the expedient was resorted to of keeping the blood fluid in the anterior chamber, instead of allowing it to clot, and then washing it out. This was accomplished by the use of sodium citrate solution injected into the anterior chamber. In the later operations neo-synephrin hydrochloride was used. Some animals showed fresh bleeding after being returned to the cage from the operating room, and practically all of these animals had finally to be discarded.

With this technic, approximately 50 per cent of the animals recovered completely and were used for subsequent experimentation, but only if the eye was entirely free from any signs of inflammation. In many of the animals the cornea showed scarring at the limbus, but no animals were used in which there was any vascularization of the cornea. The anterior segments were otherwise normal, and all animals were examined with the slit lamp. The ocular fundus was found to be normal in all instances. A few of the eyes were removed for histologic study.

TABLE 1.—*Intraocular Pressure and Volume of Anterior Chamber After Iridectomy*

	Tension		Volume of Anterior Chamber	
Cat No.	Eye Operated on, Mm. Hg	Control Eye, Mm. Hg	Eye Operated on	Control Eye
107	11	29	0.35 cc.	0.8 cc.
			0.2	0.7
101	13	17	0.55	0.8
			0.6	1.0
112	19	25		
136	9	22	0.4	0.8
128	19	22	0.45	0.7
	17	22		
117	11	22	0.5	0.8
	15	22		
122	17	22	0.2	0.9
88	..	..	0.4	1.0
			0.2	0.7
91	..	..	0.2	0.8
93	..	..	0.2	0.7
92	..	..	0.2	0.85
127	..	..	0.6	1.0

Dr. Wilfred Fry, who examined several of them, reported no evidence of cyclitis or choroiditis and no intraocular inflammation. The ciliary bodies were intact. The anterior chambers were clear. There were no keratic precipitates, and the iris had been completely torn away from its base in all the sections examined.

After a month or more those animals which were considered suitable were given sodium amytal intraperitoneally and the tension of both eyes measured. Then the aqueous was evacuated completely from each eye with a fine syringe. The amount of fluid obtained was considered to give an approximate measure of the volume of the anterior chamber. Table 1 shows the results in a series of cats. In every instance the volume of the anterior chamber was considerably reduced in the iridectomized eye, and, presumably as a direct result of the diminished volume of the globe, the intraocular tension was lowered.

The protein content of the aqueous was then determined in the iridectomized and in the control eyes. The analyses were made by the turbidometric method of Looney and Walsh.[4]

4. Looney, J. M., and Walsh, A. I.: Determination of Spinal Fluid Protein with Photoelectric Colorimeter, J. Biol. Chem. **127**:117, 1939; Determination of Globulin and Albumin in Blood Serum by Photoelectric Colorimeter, ibid. **130**:635, 1939.

Table 2 shows the results of the analyses in 4 cats. In 3 of the 4 cats the protein content of the eye operated on was nearly identical with that of the control eye. In cat 91 the protein content was higher, but this cat was not completely iridectomized. This is additional proof that the operations were free from any inflammatory effect, since it is well known that any intraocular inflammation results in an enormous increase in the protein content of the aqueous.

TABLE 2.—*Protein Content of Aqueous After Iridectomy*

Cat No.	Interval Between Operation and Experiment	Milligrams of Protein per 100 Cc.	
		Eye Operated on	Control Eye
88	5 months	20	22
88	8 months	11.7	16.6
91	3 months	52	17.5
101	3 months	18	19.6
101	7 months	11.8	16
112	7 months	29.6	24.4

TABLE 3.—*Protein Content of the Secondary Aqueous After Iridectomy*

Cat No.	Interval Between Operation and Experiment	Milligrams Protein per 100 Cc.				Time of Formation of Secondary Aqueous
		Primary Aqueous		Secondary Aqueous		
		Eye Operated on	Control Eye	Eye Operated on	Control Eye	
117	7 months	60	18.3	535	3050	28 minutes
107	10 months	33.3	21.9	1216	2220	30 minutes
127	5 months	21.3	25.6	892	3000	34 minutes
101	13 months	23.3	26.1	578	1706	35 minutes
136	2 months	32	15.7	350	3210	37 minutes
88	7 months	14.7	20.3	122	747	45 minutes
101	5 months	12.8	14.8	495	2225	45 minutes
107	10 months	46.5	18.5	241	2415	47 minutes
107	3 months	43.3	152	13.8	169	25 hours

TABLE 4.—*Urea Content of the Aqueous After Iridectomy*

Cat No.	Milligrams of Urea per 100 Cc.			Percentage of Urea, Aqueous/Serum	
	Serum	Aqueous of Eye Operated on	Aqueous of Control Eye	Eye Operated on	Control Eye
87	29	27	22.6	93.2	77.9
88	33.1	31.1	26.6	94	80.4
88	....	44.6	41.4	....	....
88	....	47.1	42.2	....	....
91	28.8	27.6	21.1	95.8	73.3
91	....	39.8	34.2	....	....
92	....	30	30	....	....

In a number of these animals the anterior chambers were allowed to reform and the secondary, or plasmoid, aqueous removed and its protein content analyzed. The results are shown in table 3.

These figures indicated that the enormous increase in the protein content of the secondary aqueous comes largely from the blood vessels of the iris itself. The fluid which reforms in the iridectomized eye has a higher protein content than the original aqueous, but never approaches that in an eye with an attached iris.

In a series of cats the urea content of the aqueoous was determined, the chemical methods reported in the previous paper [1] being used. In some of these cats a sample of blood was withdrawn simultaneously by cardiac puncture and its urea

content determined also. Table 4 gives the results. In all the animals the slightly higher urea content of the iridectomized eye may have been due simply to the free contact of the aqueous with the posterior part of the eye, from which it is normally excluded by the iris. It is known that the level of urea in the vitreous more nearly approaches that of blood than does the level in normal aqueous.[5]

COMMENT

The iris was removed in a series of cats without causing any apparent permanent damage to the eyes. When completely recovered from the operation, these eyes show a number of interesting features: The volume of the anterior chamber was considerably reduced, being approximately 40 per cent less than normal. The tension was reduced 60 per cent below normal. This reduction in tension was most likely the direct result of the diminished volume of the anterior chamber. Why does removal of the iris cause a reduction of about half the volume of aqueous humor? There are obviously a number of possible explanations, and the present state of knowledge does not allow us to do more than mention some of these. The iris itself may be concerned with the formation of normal aqueous. There is no reason to believe that the meshwork of blood vessels in the iris cannot be looked on as a filtering surface, permitting an interchange of fluid between blood and aqueous. It seems certain as a result of these experiments that the enormous increase in protein in the secondary aqueous comes largely from the vessels of the iris, for in the iridectomized eye the protein content rises to a much smaller degree.

A number of practical points are suggested by these results. When there has been a hemorrhage into the anterior chamber as a result of trauma, it is probably better not to dilate the pupil, since the absorption of blood seems to depend on the presence of the iris stroma. A basal iridectomy for glaucoma not only should be basal but should be broad. Part of the effect may be the elimination of a portion of the filtering surface as well as freeing of the chamber angle.

313 South Seventeenth Street.

DISCUSSION

Dr. Peter C. Kronfeld, Chicago: There is a limit to the amount of aqueous that can be withdrawn from the human eye. Toward the end of the aspiration the iris comes in contact with the cornea or is sucked into the tip of the needle. This can be avoided if the opening of the needle is made to face the cornea, yet even with the needle remaining unblocked one reaches a point at which no more fluid can be obtained by moderate suction. In certain eyes which are definitely diseased, however, the amount of fluid which can be aspirated is almost unlimited, fluid vitreous rapidly replacing the aqueous. In a recent paper by Irvine Jr., of Los Angeles (*Am. J. Ophth.* **25:** 162, 1942), this phenomenon was described in detail. The fact that the amount of aspirable aqueous was definitely limited in the eyes on which Dr. Adler and associates performed complete iridectomies is an argument, I believe, in favor of the normal, intact status of those eyes, anatomically as well as functionally.

I should like to ask Dr. Adler whether he can give figures on the rate at which the intraocular fluid was reformed after aspiration of the primary aqueous in the iridectomized eyes.

Dr. Francis Heed Adler, Philadelphia: The rate of reformation was approximately the same in the iridectomized eyes as in the normal eyes. However, it is more difficult to determine the rate in an eye in which the iris has been removed, because it is more difficult to note the beginning reformation of the chamber without a background like the iris from which to judge the depth of the chamber. Within half an hour we were able to obtain sufficient fluid to begin our analyses.

5. Adler, F. H.: Is Aqueous Humor a Dialysate? Arch. Ophth. **10**:11 (July) 1933.

STRUCTURAL CHANGES IN EXTERNAL GENICULATE BODY OF RAT FOLLOWING REMOVAL OF EYES

ROBERT R. CHACE, M.D.
PROVIDENCE, R. I.

For many years research has been carried out on the problem of the cellular response in the developing nervous system to the presence or absence of peripheral stimuli. Detwiler,[1] working with amphibian larvae, demonstrated the hyperplasia of sensory ganglions when they were connected with a transplanted limb. That the central nervous system responds to increased peripheral stimuli by an excessive proliferation of cellular elements has been demonstrated clearly by Burr,[2] who showed that there is a definite hyperplasia in the pars dorsalis thalami and in the cerebral hemisphere when an additional nasal placode is grafted adjacent to the normal one in Amblystoma. Further, Hamburger [3] showed that the motor horn areas of the cord underwent a hyperplasia when limb primordia were grafted in chick embryos. The opposite procedure, removal of an end organ, has been shown to bring about a hypoplasia in the central nervous system, in the frog by May [4] and in the chick by Hamburger.[5]

In a consideration of these responses of the central nervous system to increased or decreased peripheral demands, one finds that the optic pathways lend themselves admirably to a study of the variations in structure incident to such changes. If one destroys an optic nerve or removes an eye, there is a somewhat progressive transformation in the visual pathway. There seems to be no uniformity in the literature as to just

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From the Department of Anatomy, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

Prof. Samuel R. Detwiler, Department of Anatomy, gave helpful suggestions and guidance in the carrying out of this study.

1. Detwiler, S. R.: On the Hyperplasia of Nerve Centers Resulting from Excessive Peripheral Loading, Proc. Nat. Acad. Sc. **6**:96-101, 1920.

2. Burr, H. S.: Hyperplasia in the Brain of Amblystoma, J. Exper. Zoöl. **55**:171-191, 1930.

3. Hamburger, V.: Motor and Sensory Hyperplasia Following Limb-Bud Transplantations in Chick Embryos, Physiol. Zoöl. **12**:268-284, 1939.

4. May, R. M.: Modifications des centres nerveux dues à la transplantation de l'oeil et de l'organe olfactif chez les embryons d'Anoures, Arch. de biol., Paris **37**:335-396, 1927.

5. Hamburger, V.: The Effects of Wing Bud Extirpation on the Development of the Cerebral Nervous System in Chick Embryos, J. Exper. Zoöl. **68**:449-494, 1934.

how far back from the eye the changes extend, nor is the difference in opinion confined to workers using only animals. From clinical reports of cases of anophthalmia and severe microphthalmia, there is the same confusion. Although many cases of anophthalmia and microphthalmia are on record, there have been few cases in which enucleation, which would permit some histologic study of the optic nerve stump, was performed and still fewer cases in which there was an autopsy with a careful study of brain sections. As a result, there is much that is not known about the retrograde changes.

Von Monakow [6] enucleated the eyes of rabbits, cats and dogs and found degeneration of the optic nerve on the side operated on, in the chiasma and in the tract on the contralateral side. In addition, he found a degeneration of the superior colliculus and the lateral geniculate body, but no changes in the visual cortex, except in 1 animal.

Van Duyse [7] reported on a child with bilateral anophthalmia who died at 3 months. At postmortem examination it was found that the optic nerves were absent, the optic tracts defective and the external geniculate bodies poorly defined, as were the anterior corpora quadrigemina. Monthus [8] reported a case of microphthalmia in a term infant whose optic nerves were normal in spite of the fact that the microphthalmia was severe. (It should be kept in mind that there are few cases of real anophthalmia, careful dissection showing in most cases small globular masses of tissue in the orbits, which prove the anomaly to be an extreme form of microphthalmia.) Hanke [9] described a case of bilateral anophthalmia with optic tracts and chiasma completely missing. Mayou [10] reported on a child born at 7 months and living twenty-four hours in whom the microphthalmia was bilateral but the optic nerves appeared normal at autopsy.

Bernheimer [11] studied congenital anophthalmia in rats and found the optic nerve absent or shrunken on the side of the defect. Yudkin [12]

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6. von Monakow, C.: Experimentelle und pathologisch-anatomische Untersuchungen über die Beziehungen der sogenannten Sehsphäre zu den infracorticalen Opticuscentren und zum Nervus opticus, Arch. f. Psychiat. **14**:699-751, 1883.

7. Van Duyse, G. M.: De l'anophtalmie congénitale, Arch. d'opht. **19**:412-429, 1899.

8. Monthus, N. M., and Opin: Étude histologique et pathogénique d'un cas de microphtalmie, Arch. d'opht. **23**:32-50, 1930.

9. Hanke, V.: Zwei seltene Missbildungen des Bulbus: I. Anophthalmus congenitus bilateralis; II. Dermoid der Cornea und endobulbares Lipom, Arch. f. Ophth. **57**:28-52, 1903.

10. Mayou, M. S.: Microphthalmos, Tr. Ophth. Soc. U. Kingdom **24**:340-357, 1904.

11. Bernheimer, S.: Anophthalmus congenitus und die Sehbahn, Arch. f. Ophth. **65**:99-105, 1906.

studied 4 rats born without eyes and found no sign of an optic nerve. Later he [13] described a microphthalmic child who on postmortem examination showed optic nerves consisting of fibrovascular tissue. Tsang,[14] after peripheral blinding of rats, found an atrophy of the optic nerve, chiasma and tract with a reduction in size of the external geniculate body. Whitnall and Norman [15] found in a microphthalmic child, in whom the eyeballs were completely disorganized, a poor development of the optic nerves, chiasma tracts and external geniculate bodies, but normal development of the superior colliculi and optic radiations.

In view of the apparent confusion in the literature as to the changes occurring in the geniculate bodies after enucleation (or severe disorganization of the globe), an investigation was carried out in an effort to determine whether the reduction in size of these bodies is brought about by atrophy or hypoplasia or both.

II. MATERIAL AND METHODS

A. Material.—In these experiments the common white, or hooded, laboratory rat was used. The animals varied from newborn rats to adult rats 1 year old. The rat was chosen because considerable work has been done already on this mammal with regard to the optic pathways, so that a careful comparison with the work of previous investigators was possible. In addition, rats are small enough to be housed conveniently in large numbers and are relatively inexpensive. A further reason for their use was that 2 rats in the animal colony had been born apparently anophthalmic and at the time of the investigation were 1 year old. Thus they provided a starting point for the work.

B. Anesthesia and Operations.—All surgical work was done with ether anesthesia. When completely anesthetized, the animals were laid on a table, and the left eyes of the adults were enucleated with scissors and forceps. No attempt was made to clean the operative field, but the instruments were dipped in alcohol before being used. Bleeding was controlled by pressure on the lids with a cotton swab, and the blood clotted almost at once. The rats were then returned to their cages, and they recovered from the anesthesia within thirty minutes. No instances of infection were noted. Newborn rats were anesthetized by means of a cotton swab soaked with ether and held before their noses for a minute or two. Little anesthesia was required. In the newborn rats enucleation of the right eye was performed, and

12. Yudkin, A. M.: Congenital Anophthalmos in a Family of Albino Rats, Am. J. Ophth. **10**:341-345, 1927.

13. Yudkin, A. M.: Congenital Bilateral Microphthalmos Accompanied by Other Malformations of the Body, Am. J. Ophth. **11**:128-131, 1928.

14. Tsang, Y. C.: Visual Centers in Blinded Rats, J. Comp. Neurol. **66**: 211-251, 1937.

15. Whitnall, S. E., and Norman, R. M.: Microphthalmia and Visual Pathways: Case Associated with Blindness and Imbecility and Sex-Linked, Brit. J. Ophth. **24**:229-244, 1940.

this was done most conveniently with a small keratome, which shelled the eye out of the socket.

C. Classification of Groups Studied.—The rats were grouped as (1) normal adult rats 1 year of age, (2) adult anophthalmic rats 1 year of age, (3) rats with the right eye enucleated at birth (these animals were studied at varying periods up to one year postoperatively) and (4) adult rats with the left eye enucleated one year after birth and studied at varying intervals up to one year postoperatively.

D. Preparation of Material for Study.—The animals to be studied were anesthetized with ether. Each animal was then laid on its back, and an incision was made in the thorax exposing the heart. The apex was seized with toothed forceps and the heart withdrawn through the wound. By means of a no. 18 needle and a 20 cc. syringe, a solution of 10 per cent solution of formaldehyde neutralized with sodium carbonate was injected into the left ventricle. This caused perfusion of the entire vascular system with formaldehyde. Cessation of respiration was practically instantaneous, and heart action ceased in a few seconds. That the entire body was perfused was shown by the fact that muscular twitchings appeared throughout the animal and the foot pads, ears and irises became blanched. Further, the neck and limb muscles took on the stiffness found in rigor mortis.

The animal was decapitated and the skin removed from the roof of the skull. The bones of the skull were now crushed with a bone forceps and the fragments removed carefully, the operator using a binocular loupe. With the entire brain exposed and the bony tentorium removed, the olfactory bulbs were cut flush with the frontal lobes and the anterior portion of the brain lifted up. The various nerves were exposed and cut with fine scissors, so that the brain could be lifted upward to a greater extent. The optic nerves were then cut just anterior to the chiasma and the brain tipped back until it was entirely out of the skull. The spinal cord was cut with scissors just below the medulla and the brain suspended by a cotton thread in a bottle containing 10 per cent neutral solution of formaldehyde. The brain was kept in formaldehyde solution for twenty-four hours and, after being washed in running tap water for twenty-four hours, was passed through solutions of pyroxylin of increasing density, the cold technic being used.

E. Histologic Technic.—Serial sections, in many instances, were cut from the chiasma back through the external geniculate body at a thickness of 12 to 14 microns. Other specimens were sectioned only through the region of the external geniculate body. These sections were stained with erythrosin-eosin for cellular detail; certain sections were prepared with Nissl stain, while others received the iron-hematoxylin stain (a solution of ferric alum being used as a mordant), which was especially good for fiber tracts.

III. GROSS STUDIES

The anatomy of the optic pathway in the rat has been worked out by Lashley.[16] He showed that the greater part of the fibers of the optic nerve decussate. This being the case, the study of the changes in the external geniculate body following enucleation of the eye is

16. Lashley, K. S.: Mechanism of Vision: Cerebral Areas Necessary for Pattern Vision in the Rat, J. Comp. Neurol. **53**:419-471, 1931.

simplified. Lashley stated the opinion that the optic tracts lead directly to the external geniculate bodies, whereas Tsang stated the belief that most of the fibers terminate in the superior colliculus.

In the present study 19 rats were operated on the day of birth, both eyes being removed. Beginning at two weeks after operation, and thereafter at frequent intervals up to one year, the animals were killed and gross studies made of the brain, including a comparison with normal control animals, of which there were 2 (fig. 1). At two weeks there was no gross evidence of the optic nerves, nor was there any at a later time. There was also no gross evidence of chiasma or tracts.

Fig. 1.—Ventral surface of the brain of a normal adult rat.

In addition to this material, there were 2 animals born, to all appearances, without eyes. The lids were closed and sank into the sockets. Both rats were adults 1 year of age. One of the animals had on the right side in place of an eye a small, shrunken expansion of the optic nerve ending in a funnel-shaped structure. On the left side, deep in the socket, was an eye about 2 mm. in diameter, with a clear cornea but no lens. The optic nerves extended back toward the region of the chiasma for a few millimeters and showed a definite fiber pattern. The nerves then became gelatinous strands and lost themselves in the general direction of the chiasma, which could not be demonstrated. The second animal showed no evidence of eyes, nerves, chiasma or tracts. The appearance of the

Fig. 2.—Brain of a rat born eyeless compared with a normal brain.

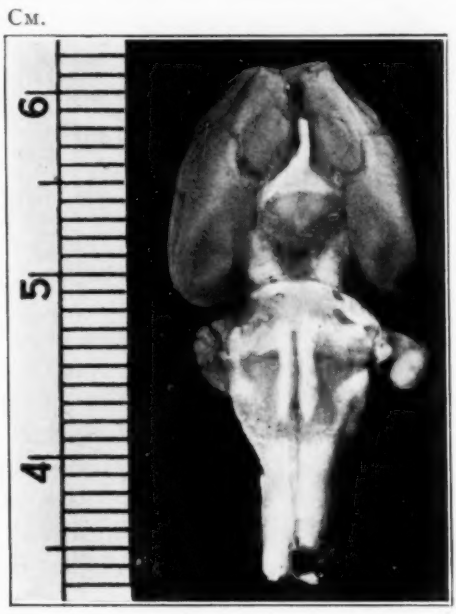

Fig. 3.—Brain of an adult rat with an eye removed at birth.

ventral surface of the brains of these animals when compared with those of the normal animals was striking (fig. 2).

For a better comparison, 8 animals were operated on the day of birth, the right eye being enucleated. Observations were made on the brains at one week, two weeks and one, two, four, six, nine and twelve months postoperatively. At one week the optic nerve was found to be considerably smaller on the right than on the side not operated on. At two weeks the optic nerve was missing, and it was lacking thereafter in all specimens (fig. 3).

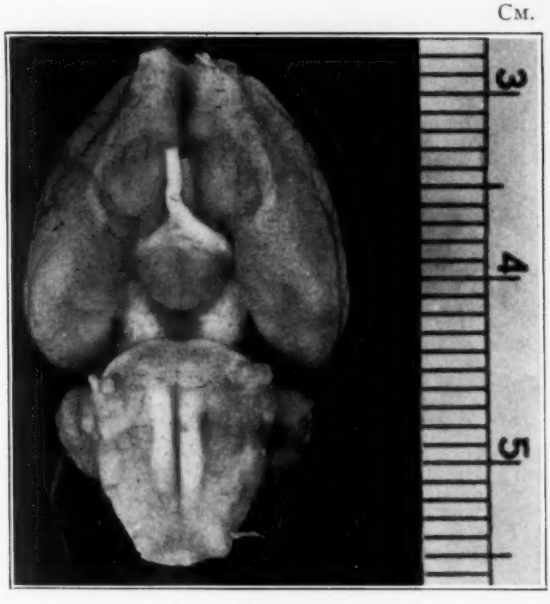

Fig. 4.—Brain of an adult rat with an eye removed one year previously.

In addition, the left eye of 6 adult rats was enucleated, and the brains were studied at one, three, six and twelve months, respectively, after operation. At one month the chiasma and tracts were found to be normal in appearance, whereas the nerve leading to the socket of the enucleated eye was not quite as white as the normal nerve. At three months the nerve to the side operated on was of smaller volume and somewhat translucent. This appearance was even more striking at six months. However, grossly there was no change in the appearance of the chiasma or tracts. At one year the nerve to the side operated on was reduced to a tiny thread of clear gelatinous material and the chiasma was somewhat smaller (fig. 4). The optic tracts were of normal appearance grossly.

IV. MICROSCOPIC STUDIES

Besides being studied grossly, the brains of some of these animals were examined microscopically. Cell counts were made in three separate regions of the geniculate body on both sides of the section, and three sections were studied in each instance. A Zeiss micrometer was used which measured 5 mm. on a side and was further subdivided into squares of 0.5 mm. on a side. All nerve cells appearing in the large square were counted. With an eyepiece producing a magnification of 10 and an objective of 43 on the microscope, a magnification of 430 was obtained. Calibration of the eyepiece micrometer against a stage micrometer ruled

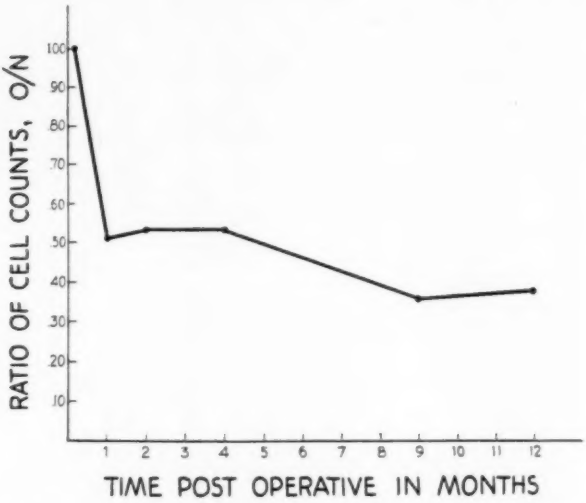

Fig. 5.—Graph showing the ratio of cell counts in the external geniculate body of the rat after removal of an eye at birth.

one hundred lines to the millimeter shows that 1 mm. on the eyepiece micrometer is equal to 0.066 mm. (or 66 microns) on the stage micrometer. Since 5 mm. would equal 0.33 mm. on the stage, the area of the tissue contained within the large square would be 1,089 square millimeters, or 108,900 square microns.

Animals in which the right eye had been removed at birth showed no cellular reduction in the external geniculate body of the corresponding side at one week after operation. It will be noted (table 1) that rather high cell counts were obtained. Cells were found to be relatively undifferentiated at this stage, and it was difficult to distinguish between nerve cells and supporting cells. It will be seen from the table and the graph (fig. 5) that a cellular change occurs after one month, with a con-

siderable reduction in the number of cells on the side corresponding to the eye operated on. The ratio of cells on the normal side to that on the side operated on is high. For from one to nine months there is a further drop in the number of cells, with no essential change thereafter up to and including one year. In addition to changes in the geniculate

TABLE 1.—*Cell Counts in Given Areas of the Geniculate Bodies in Animals with One Eye Removed at Birth and Killed at Varying Intervals*

Animal	Time	Overage Cell Counts *		Ratio	
		Normal Side	Side Operated On	Normal Side	Side Operated On
14	1 week	70	69	1.00 :	0.98
18	2 weeks	70	70	1.00 :	1.00
21	1 month	41	21	1.00 :	0.51
23	2 months	43	23	1.00 :	0.53
24	4 months	39	21	1.00 :	0.53
29	9 months	38	14	1.00 :	0.36
31	1 year	34	13	1.00 :	0.38

* Each average count is based on three separate counts for the normal side and the side operated on, in three separate sections.

TABLE 2.—*Cell Counts of the Geniculate Bodies of a Normal Rat Compared with Those of Animals Born Without Eyes*

Animal	Time	Average Cell Counts		Ratio	
		Right Side	Left Side	Right Side	Left Side
3	1 year (normal)	39	38	1.00 :	0.97
1	1 year (blind)	14	14	1.00 :	1.00
2	1 year (blind)	15	14	1.00 :	0.93

TABLE 3.—*Cell Counts in Given Areas of the Geniculate in Animals with One Eye Removed One Year After Birth and Killed Six and Twelve Months Later*

Animal	Time	Average Cell Counts		Ratio	
		Normal Side	Side Operated On	Normal Side	Side Operated On
27	6 months	32	30	1.00 :	0.93
33	1 year	33	33	1.00 :	1.00

bodies, there is a noticeable change in the appearance of the tracts (figs. 6 and 7).

A comparison of the cell counts for a normal animal and one born "eyeless" and killed at 1 year of age showed a reduction in cells in the latter but no difference on the two sides (table 2). The reduction in size of the optic tracts was pronounced (fig. 8).

Adult animals with an eye removed at the age of 1 year and killed six or twelve months afterward (table 3) showed no reduction or other difference in cell count between the two sides.

V. COMMENT

From these results it is apparent that in the rat, enucleation of the eye if done at birth, while the external geniculate bodies are not fully

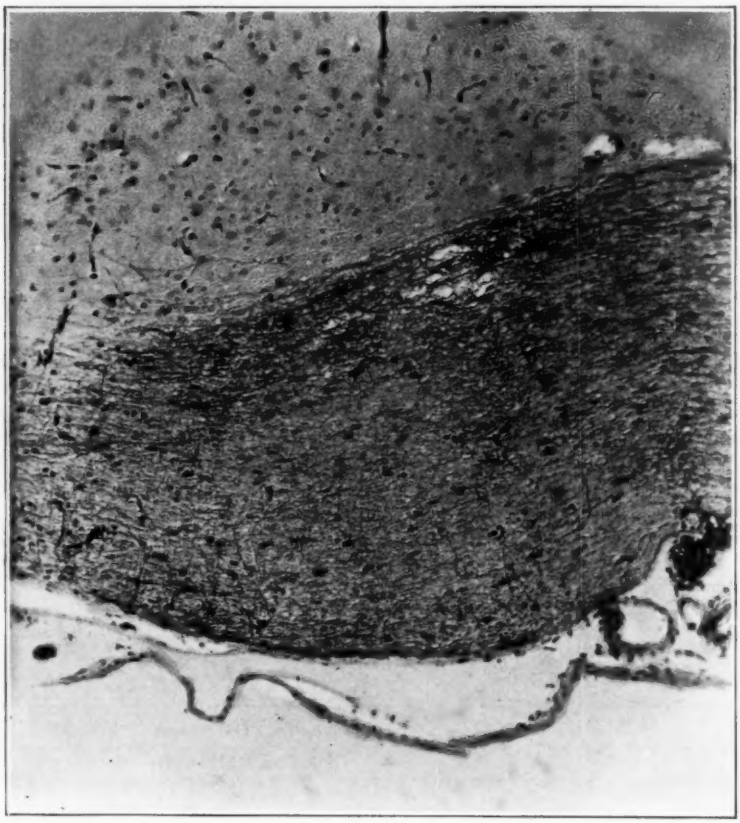

Fig. 6.—Optic tract of a normal adult rat (× 140).

developed, will promote a hypoplastic development of these centers. This phenomenon is best studied by means of serial sections or at least closely adjacent sections. As cell differentiation proceeds, there is a definite lag in cell proliferation on the side of the brain operated on as compared with the normal side. That it is not atrophy alone can be seen by a careful study of the appearance of the cells, which are normal

in size and have undergone the usual differentiation. There does not seem to be any cellular abnormality. After six months there is a further reduction in the number of nerve cells and cell nuclei of odd shapes are seen. During all this time there is no apparent effect on the number or appearance of the glial cells. The reduction in the number of the nerve cells, in addition to atrophy following disuse, would account for

Fig. 7.—Optic tract of an adult rat with the right eye removed at birth (× 140).

the decreased size of the geniculate bodies, as measured by Tsang [14] after enucleation of the eye in the rat.

Animals born "eyeless" (actually having extreme forms of microphthalmia) showed a bilateral reduction in the number of nerve cells in the geniculate bodies, as would be expected from a bilateral enucleation at birth. On the other hand, removal of an eye of an adult rat, while causing some atrophy of the optic nerve on that side, appeared to have no effect on the chiasma, optic tract or external geniculate body.

VI. SUMMARY

1. Removal of one eye from a newborn rat causes degeneration of the optic nerve and tract corresponding to that eye. The corresponding external geniculate body undergoes a hypoplastic development (table 1).

2. The brains of rats born with microphthalmic or degenerated eyes lack optic nerves, chiasmas and tracts, and the external geniculate bodies exhibit a definite hypoplasia (table 2).

Fig. 8.—Optic tract of an adult rat born apparently eyeless (× 140).

3. Removal of one eye in an adult animal is followed by atrophy of the optic nerve. Gross changes have not been noted in the chiasma or optic tract, nor any microscopic alterations in the external geniculate body (table 3).

415 Wayland Avenue.

HOMATROPINE-PAREDRINE EMULSION AS A CYCLOPLEGIC

ELTON YASUNA, M.D.
WORCESTER, MASS.

In 1937 Myerson and Thau,[1] in Boston, suggested that benzedrine sulfate might be useful in producing cycloplegia, since it produces excellent mydriatic action. Accepting this suggestion, Beach and McAdams,[2] in Maine, set up a study of benzedrine sulfate and combined this drug with 1 per cent atropine sulfate solution and also 5 per cent homatropine hydrobromide solution. In a small number of cases these combinations were used as cycloplegics, and the authors concluded that the time required to obtain cycloplegia was decreased, while the recovery time for the patient was considerably reduced. In general about forty to sixty minutes was required for complete cycloplegia when atropine sulfate solution followed by benzedrine sulfate solution was employed.

The work of Beach and McAdams was confirmed by Powell and Hyde,[3] who in two articles reported good results from 2 per cent homatropine solution with 1 per cent benzedrine sulfate solution.

Late in 1937, however, paredrine hydrobromide (p-hydroxy-α-methylphenethylamine hydrobromide) was developed, a substance whose chemical structure resembles that of benzedrine. A series of studies was begun in which this drug was used in combination with the usually employed cycloplegics. The first study reporting on an appreciable number of subjects (73) appeared in September 1938. In this study, by Tassman,[4] 1 drop of 5 per cent homatropine hydrobromide solution or of 1 per cent atropine sulfate solution was used and was followed in three minutes by 1 drop of "1 per cent aqueous solution of paredrine hydrobromide." He concluded that the combination produced effective cycloplegia with the comparatively rapid recovery time of about eight hours. The preparation was not irritating, did not affect intraocular tension and, except for a transient mild blanching of the conjunctiva, produced no undesirable reactions.

This work was taken up by others, and late in 1938 and early in 1939 several papers appeared substantiating the work of Tassman. Perhaps the best of these were the reports of Shemeley[5] and, later, of Weinman and Fralick.[6]

Dr. Yasuna was formerly resident in the Ophthalmic Service of the Boston City Hospital.

This paper was presented before the New England Ophthalmological Society, March 17, 1942.

1. Myerson, A., and Thau, W.: Human Autonomic Pharmacology, Arch. Ophth. **18**:78-90 (July) 1937.

2. Beach, S. J., and McAdams, W. R.: Benzedrine in Refraction, Tr. Am. Ophth. Soc. **35**:221-226, 1937; Benzedrine in Cycloplegia, Am. J. Ophth. **21**:121-124 (Feb.) 1938.

3. Powell, L. S., and Hyde, M. E.: Effect of Benzedrine Sulfate Solution on Cycloplegia, J. Kansas M. Soc. **39**:1-4 (Jan.) 1938; Action of Eserine Administration During Homatropine-Benzedrine Cycloplegia, ibid. **39**:57-59 (Feb.) 1938.

4. Tassman, I. S.: The Use of Paredrine in Cycloplegia, Am. J. Ophth. **21**:1019-1024 (Sept.) 1938.

5. Shemeley, W. G., Jr.: Paredrine Hydrobromide for Cycloplegia, Eye, Ear, Nose & Throat Monthly **18**:279-282 (Oct.) 1939.

6. Weinman, E. B., and Fralick, F. B.: Comparative Study of Benzedrine, Paredrine and Cocaine with Homatropine as Cycloplegics, Am. J. Ophth. **23**:172-178 (Feb.) 1940.

In spite of these favorable reports several questions arose, and the use of paredrine with atropine or homatropine was not accepted extensively by ophthalmologists. Evidence was not conclusive as to whether the addition of paredrine hydrobromide produced quicker and more transient relaxation of accommodation than use of atropine or homatropine alone.

Further studies were contributed by Tassman,[7] Thorne and Murphy[8] and Weinman and Fralick,[6] who found that the residual accommodation in small numbers of cases after the use of paredrine hydrobromide with atropine sulfate in aqueous solution was about 1 D. or, possibly, a little less. Several workers[9] had shown that paredrine hydrobromide alone had no cycloplegic action. Therefore, its action in combination with the cycloplegics might well be a synergistic one if a greater relaxation of accommodation resulted.

During 1941 several ophthalmologists in Boston tried the addition of 1 drop of a 1 per cent aqueous solution of paredrine hydrobromide[10] three minutes after the use of 1 drop of 1 per cent atropine sulfate solution or of 5 per cent homatropine bromide solution but did not find use of this combination superior to the original methods. It was at this time that Dr. James J. Regan, chief of the ophthalmic service at the Boston City Hospital, suggested a clinical study of the product. He persuaded Smith, Kline & French Laboratories to combine homatropine and paredrine in an emulsion. The study was begun during 1941, and it differed in three respects from that of any previous report.

Firstly, the aqueous solution of paredrine hydrobromide was not used. Instead an emulsion was made up according to the following formula:

Paredrine hydrobromide	1 Gm.
Homatropine hydrobromide	4 Gm.
Acacia	12.5 Gm.
Liquid petrolatum	25 Gm.
Glycerin	2 Gm.
Merthiolate	0.001 Gm.
Water to make	100 cc.

The emulsion was made in a homogenizer in order to obtain a better suspension. It was felt that with an emulsion the cornea and conjunctiva would be coated for many minutes before tears washed it away. Thus a prolonged action would be produced. With the aqueous solution a portion of the preparation went down the nasolacrimal duct when put in the eye, but the thick consistency of the emulsion minimized this loss. In appearance the preparation resembled white liquid shoe cream.

Secondly, refraction was performed on each subject with the cycloplegic alone, either atropine sulfate or homatropine hydrobromide, and then with the homatropine-paredrine emulsion. An interval of two to three weeks elapsed between the examinations, allowing time for the effect of the first cycloplegic to disappear. The subjects chosen were from the patients of the ophthalmic clinic of the Boston City Hospital. The procedure with atropine consisted in the use

7. Tassman, I. S.: The Clinical Uses of Paredrine Hydrobromide in the Eye, Pennsylvania M. J. **44**:191-194 (Nov.) 1940.

8. Thorne, F. H., and Murphy, H. S.: Cycloplegics, Arch. Ophth. **22**:274-287 (Aug.) 1939.

9. (*a*) Abbott, W. O., and Henry, C. M.: Paredrine: A Clinical Investigation of a Sympathomimetic Drug, Am. J. M. Sc. **193**:661-672 (May) 1937. (*b*) Mayer, L. L.: Dilation of the Pupil for Ophthalmoscopic Examination, J. A. M. A. **113**:38-39 (July 1) 1939. (*c*) Laval, J.: Allergic Dermatitis and Conjunctivitis from Paredrine Hydrobromide, Arch. Ophth. **26**:585-586 (Oct.) 1941.

10. Paredrine hydrobromide ophthalmic was used: paredrine hydrobromide 1 per cent in distilled water made tear isotonic with 2 per cent boric acid and preserved with merthiolate 1:50,000.

of a 0.5 per cent atropine sulfate ointment three times daily for three days before the examination. With homatropine, 1 drop of a 2 per cent solution of homatropine hydrobromide was instilled every ten minutes for one hour. When the emulsion containing paredrine was used, 1 drop was placed in the lower cul-de-sac, with no further medication.

The third difference between this and other studies was in the type of subjects selected. The great majority had moderate or severe hyperopia, and a number with esotropia were included. Only children under 16 were accepted, and no child under 7 was used, because a certain amount of cooperation was desirable. This type of subject was selected because it was felt that the young hyperope with or without concomitant convergent strabismus afforded the most critical medium for the evaluation of the paredrine-homatropine combination. The amount of residual accommodation in each case was measured twice, once after refraction with atropine or homatropine alone and again after refraction with the emulsion.[10a]

RESULTS

A total of 50 subjects were studied, but these represented only 92 separate eyes, since 8 eyes were amblyopic. Twenty-four subjects were studied with homatropine hydrobromide and 26 with atropine sulfate (46 eyes in each group); 37 subjects had hyperopia (12 of more than 3 D.), 6 myopia, 21 astigmatism, 4 emmetropia and 7 esotropia. Most of the subjects with astigmatism were also classified in the groups with hyperopia or myopia. A subject who needed 0.75 D. of cylinder for each eye or 1.00 D. or more for either eye was classified as astigmatic. Subjects requiring less cylinder than this were considered as predominantly hyperopic or myopic and were not classified as astigmatic. In the 7 subjects with esotropia the error ranged from 15 to 35 degrees.

Forty-six per cent of the subjects studied with atropine sulfate accepted more plus sphere with this cycloplegic than with paredrine-homatropine emulsion; 19 per cent accepted less plus sphere, and in 35 per cent the results were identical. The group studied with homatropine hydrobromide accepted an average of 0.14 D. more plus sphere with this cycloplegic than with the paredrine-homatropine emulsion; 52 per cent accepted more plus sphere with the emulsion and 13 per cent accepted less, while in 35 per cent the results were identical.

Paredrine-Homatropine Emulsion	Homatropine (46 Subjects)	Atropine (46 Subjects)
Average difference in sphere.....	+ 0.12 D.	— 0.14 D.
More plus sphere.....	21 subjects	6 subjects
Less plus sphere.....	9 subjects	24 subjects
Same amount	16 subjects	16 subjects

These data suggest that atropine alone produces the best relaxation of accommodation, but that the addition of paredrine to homatropine causes greater

10a. The method used for the measurement of the residual accommodation was suggested by Dr. Elek Ludvigh II, of the Massachusetts Eye and Ear Infirmary. The patient was made emmetropic for distance with the necessary lenses. Jaeger 1 print was placed 50 cm. from the eye if the vision was 20/20, and a + 3 D. sphere was added to the emmetropic correction. The plus sphere was then decreased 0.25 D. at a time until the print could be made out. The result was usually found to be + 2 D. over the distance correction, and this amount of lense corresponded to the far point in terms of dioptric strength.

Minus spheres were now added until the Jaeger print could not be made out. This was the near point. The difference between the far and the near point as expressed in diopters was the amount of residual accommodation. In this manner no movement of the printed matter was necessary. The size of the Jaeger print used depended on the amount of vision present in the eye when it was tested for distance.

relaxation than homatropine alone. However, the actual amount of residual accommodation was measured, and chart 1 shows the diopters of remaining accommodation of each subject during cycloplegia induced by the emulsion. Of the subjects, 82 per cent showed between 0.75 and 1.5 D. of residual accommodation, while a scattered few showed less than 0.75 D. and some had more remaining accommodation than 1.5 D.

The average amount of residual accommodation during cycloplegia induced by the paredrine-homatropine emulsion was 1.32 D. The subjects who had previously been examined with atropine alone had an average of 1.03 D. of residual accommodation. The children who had received homatropine hydrobromide alone

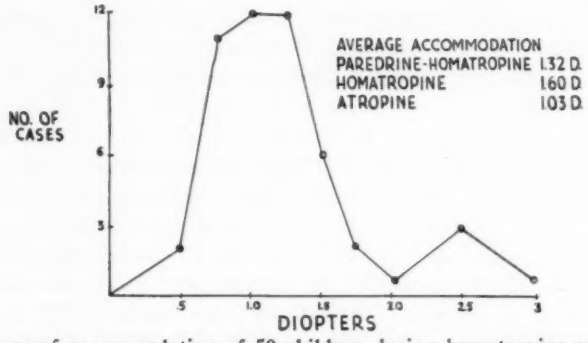

Chart 1.—Loss of accommodation of 50 children during homatropine-paredrine cycloplegia.

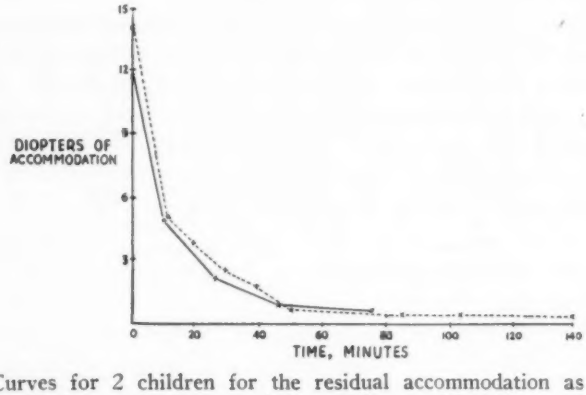

Chart 2.—Curves for 2 children for the residual accommodation as measured every ten minutes after instillation of the homatropine-paredrine emulsion.

showed the most residual accommodation, an average of 1.60 D. In most instances the two eyes showed identical amounts of residual accommodation.

In 2 children, after the instillation of 1 drop of the emulsion the accommodation was measured every ten minutes in order to determine the rate of loss of accommodation. The curves are shown in chart 2. One subject was observed for seventy-five minutes and the other for one hundred and forty minutes, and the curves were similar. After seventy minutes the maximum cycloplegic effect was obtained, and this lasted over two hours. These data suggest that the optimum time for refraction is about seventy minutes after the instillation, although one can wait at least two hours if one desires.

A study was also done to determine whether any change resulted in the amount or in the axis of astigmatism with the use of an emulsion containing paredrine. The total number of eyes examined in the group of 21 subjects classified as astigmatic was 37. Of these eyes, 10 showed a difference in axis, while the remainder did not. In all instances of variation the difference in axis was 10 degrees or less. About one half of the astigmatic eyes accepted a different amount of cylinder in the two refractions, but in 70 per cent of these the difference was only 0.25 D. There were 6 eyes which had an appreciable difference (0.50 D. or more) in the amount of cylinder accepted.

COMMENT AND CONCLUSIONS

At the time of the refraction with the homatropine-paredrine emulsion each patient was given a questionnaire, which was to be returned as soon as possible. Thirty-six patients (72 per cent) cooperated.

The first question inquired as to the length of time before the patient was able to read. The average child was able to read about sixteen hours after the instillation of the drops, and most of the answers gave a figure near this. The extremes were two and seventy-two hours. Previous determinations by Tassman [4] and by Marron [11] showed ability to read in six to eight hours. Alvaro,[12] in Brazil, suggested the use of physostigmine after the cycloplegic in order to hasten the recovery time. This procedure has also been advocated by Powell and Hyde,[13] Hartshorne [14] and Tassman,[7] in this country.

The second question concerned the length of time required for the effect of the emulsion to wear off completely. The average time in this series was twenty-four hours, with a variation from six to eighty hours. Various figures ranging from nine to twenty-four hours have been given by other authors.[15]

Specific ill effects due to the emulsion were inquired after in the third question. Thirty-three per cent of the subjects subsequently had a headache, 11 per cent were bothered by lacrimation and 11 per cent had slight pain in the eyes. In all instances the complaints were mild. One patient answered this question at some length, describing a prolonged redness and swelling of the eyelids associated with severe itching. This subsided in twenty-four hours with no ill effects. No further work-up was done on the patient, but his case calls to mind the report of Laval [9c] of a case of sensitivity to paredrine in the form of redness, dryness and scaliness of the lids after the prolonged use of the drug.

The final question asked which method of refraction was preferred. Of the subjects, 78 per cent declared a preference for use of the homatropine-paredrine emulsion, in which only 1 drop was instilled, over the use of atropine or homatropine.

In conclusion it can be stated that 1 drop of an emulsion of paredrine hydrobromide plus homatropine hydrobromide is a better cycloplegic than 1 drop of an aqueous solution of homatropine hydrobromide instilled every ten minutes for one hour. This emulsion, however, is not quite as effective as atropine sulfate

11. Marron, J.: Cycloplegia and Mydriasis by Use of Atropine, Scopolamine and Homatropine-Paredrine, Arch. Ophth. **23**:340-350 (Feb.) 1940.

12. Alvaro, M. E.: New Method of Producing Cycloplegia in Refraction, Bol. Soc. de med. e cir. de São Paulo **23**:46-51 (Feb.) 1939.

13. Powell, L. S., and Hyde, M. E.: The Practical Use of Homatropine-Paredrine Cycloplegia, J. Kansas M. Soc. **40**:251-254 (June) 1939.

14. Hartshorne, I.: The Art of Refraction, Eye, Ear, Nose & Throat Monthly **19**:201-206 (Aug.) 1940.

15. Shemeley.[5] Weinman.[6] Tassman.[7]

ointment used three times daily for three days. No axis changes in astigmatism are produced. The ill effects of the emulsion are minimal, and the majority of the children prefer its use. Finally, the emulsion is much more convenient than the older cycloplegics. A single instillation of 1 drop of the emulsion is considerably easier on both the child and the physician than repeated applications of present day cycloplegics, as currently carried out. Thus the paredrine-homatropine emulsion is the cycloplegic of choice for office practice. The curve in chart 1 suggests that refraction can be done about one hour after instillation of the emulsion.

390 Main Street.

HETEROCHROMIA OF IRIS

LEO HESS, M.D.
BOSTON

The color of the iris is known to be dependent on two pigments, one within the two epithelial layers of the posterior part of the iris (pars iridica retinae) and the other within the cells of the stroma. When only the first pigment is present, the iris appears to be blue. In gray, brown and black eyes the second pigment also is present. As to black eyes, it should be kept in mind that at the age of puberty the iris becomes slightly lighter, in contrast to the darkening of the skin and of the hair. Dark brown eyes are rare in adults of the white race. The origin of the pigment of the iris is not clearly understood. It is likely that in man, as in Amphibia, certain substances are produced in the body at a certain time of embryonic life and are carried by the blood stream into the iris, there giving rise to the formation of pigment granules. Consistent with this theory may be the fact that the irises of poorly nourished babies, especially those with severe digestive disturbances, may turn gray or brownish (de Schweinitz [1]), apparently because of lack of formation or absorption of certain substances due to the intestinal disorder. Whatever may be the origin of the pigment of the iris and whatever may be the cause of its physiologic lightening at the age of puberty and of its pathologic change in undernourished babies, the color of the two eyes in normal persons is the same. A difference in color or the presence of darker spots in one eye—heterochromia of the iris—is abnormal and needs some interpretation. This can be given only from a point of view taking into consideration the structure and the development of the entire body. I should like to mention briefly here the occurrence of heterochromia in cases of epilepsy and of chorea (Féré) and of physiologic or cyclic albuminuria (T. Harrison Butler), which suggests some general abnormality.

Many years ago Ernest Fuchs [2] pointed out that heterochromia of the iris is of two types, the first characterized merely by difference in the color of the irises, without any pathologic change either in the eyes or, apparently, elsewhere in the body (heterochromia simplex). The characteristic signs of the second type are, in addition to the difference in color, slight cloudiness of the lens and of the vitreous body and delicate precipitates in Descemet's membrane in the lighter eye (heterochromia complicata). In some cases Fuchs noticed small inflammatory changes in the choroid of the normal, i. e. the darker, eye, which indicated a deeper-seated disturbance, congenital or acquired early in life, in both eyes. Even more interesting from the standpoint of general pathology is a third type of heterochromia, in which signs of involvement of neural elements are present (heterochromia sympathica). It seems to me advisable to divide this third type into two subtypes: one in which nothing but heterochromia and a sympathetic nerve lesion (Claude-Bernard-Horner syndrome) can be found, the eyes being otherwise normal, and one in which, in addition to heterochromia and precipitates due to a cataract, sympathetic nerve lesion, ectopia of the pupil, coloboma and other abnormalities in the lighter eye are

Dr. C. Stanley Raymond, superintendent of the Wrentham State School, permitted collection at that school of some of the observations presented.

1. de Schweinitz, G. E.: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Company, 1924, p. 55.

2. Fuchs, E.: Arch. f. Ophth. **93**:381, 1917.

common. The hypothesis that in heterochromia simplex a congenital factor is essential could be supported by an observation made by Lauber.[3] He found that cats with marked heterochromia may be deaf, pigment being absent not only from the iris but from the cells of the perilymphatic tissue of the inner ear. Both the pigment of the stroma of the iris and that of the perilymphatic tissue are, according to some authors, of mesodermal origin. The lack of these pigments would consequently suggest a congenital mesodermal abnormality. In heterochromia complicata detection of occult inflammatory changes in the darker eye would point to an inborn or early acquired and slowly progressing disease. There exists a divergence of opinion as to whether the sympathetic type is congenital or acquired. An acquired lesion of the sympathetic trunk, it is generally agreed, is rarely followed by discoloration of the iris. With regard to experiments on animals with resection of one sympathetic trunk, the results of various authors are conflicting. Some found no change in the color of the iris, and others observed, along with the well known signs of a unilateral lesion, a discoloration of the iris on the side of operation. In the second subtype of heterochromia sympathica many undoubtedly congenital malformations are present.

INNERVATION OF THE IRIS

Before going into details it might be advisable to review briefly the main anatomic facts relative to innervation of the iris. The fibers of the oculomotor nerve, innervating the sphincter pupillae muscle, originate in the anteromedial group of ganglion cells of the nucleus of the oculomotor nerve (Bernheimer[4]), located in the gray substance of the floor of the aquaeductus sylvii. A short branch of the oculomotor nerve forms the so-called short root of the ciliary ganglion, where it finds a true synapse.[5] From the forepart of this ganglion arise the short ciliary nerves. They are distributed to the cornea, to the ciliary muscle and to the sphincter of the iris.

According to modern conceptions of anatomy there exists within the gray matter of the spinal cord a definite long column of ganglion cells, located in the lateral horn and in the periphery between the lateral and the dorsal horn and extending from the eighth cervical up to the upper lumbar segment (intermediolateral column). This column represents the spinal center of the sympathetic system. From it axons emerge with the anterior roots of the spinal cord and run their course to the ganglionated trunk of the sympathetic system as the so-called white rami communicantes. They are spinofugal (preganglionic fibers according to Langley[6]), their synapse being found within ganglions of the sympathetic trunk. Budge[7] was the first to state that a certain group of ganglion cells at the level of the first thoracic segment is to be considered as the spinal center of the pupil (ciliospinal center). The main part of the sympathetic preganglionic fibers of the pupil, not all of them, leave the spinal cord through the root of the first thoracic nerve. A complete paralysis of the pupil takes place, however, when, along with the fibers of the first thoracic, those of the second thoracic and the eighth cervical nerve are severed. The effect of such a lesion consists of miosis of the pupil, slight enophthalmos, lack of dilation of the pupil in response to pain (Horner's syndrome) and lack of response to local use of cocaine (which normally dilates the pupil). The same signs of sympa-

3. Lauber, H.: Ztschr. f. Augenh. **16**:254, 1906.

4. Bernheimer, S.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **107**:98, 1898.

5. Hess, L.: Pathology of Acute Glaucoma, Arch. Ophth. **26**:250 (Aug.) 1941.

6. Langley, J. N., in Schaeffer, E. A.: Directions for Class Work in Practical Physiology, London, Longmans, Green & Co., 1901.

7. Budge, J.: Ueber die Bewegung der Iris, Braunschweig, Fr. Vieweg u. Sohn, 1855, chap. 4.

thetic paralysis are present (1) after destruction of the uppermost part of the intermediolateral column, (2) after severing of the roots of the eighth cervical and the first and the second thoracic nerve and (3) after damage to the sympathetic trunk below its superior cervical ganglion, because it is at this ganglion that the sympathetic pupillary fibers reach their real synapse. Thereafter the sympathetic fibers run along the common carotid artery (within the carotid plexus, surrounding the artery) and along its branches, pass through the ciliary ganglion (without synapse) and reach, within the long ciliary nerves, the iris (postganglionic fibers according to Langley). It should be noted that the ciliospinal center is subordinated to a higher center in the corpus subthalamicum (diencephalic sympathetic center), the latter being connected with the frontal lobe (the pathway is not well known).

It is obvious that Horner's syndrome may be found frequently with (1) diffuse cerebral lesions (fracture of the skull, commotio, embolism) involving the cerebral part of the sympathetic system, (2) spinal lesions at the level of the ciliospinal, or Budge's center and (3) lesions of the sympathetic trunk.

It was necessary to mention these anatomic facts, since Horner's syndrome, heterochromia and the two signs together are not infrequently met with in children with acquired or congenital nervous diseases.

REPORT OF CASES

I. HETEROCHROMIA SIMPLEX (FUCHS)

The following tabulation contains summaries of 15 cases of heterochromia simplex:

Case No., Name, Sex, Age (Years)	Eyes	Clinical Features	Diagnosis	Comment
1 C. G. ♀ 15	Right iris dark brown; left grayish green with small brown spots	Microcephaly; forehead high; bulging; glabella broad; brows confluent	Mongolism	Ear lobes different, irregular in shape; midsternal depression; lanugo confined to sacral area; cremasteric reflex absent on both sides; patient obese (thighs and abdominal wall)
2 K. E. ♀ 28	Irises green-gray, left with green-brown hue; small cystic tumor on left upper lid	Caput quadratum; forehead bulging; frontal bosses prominent; glabella broad, flat; metopism	Athetosis; epilepsy; hydrocephalus	Ear lobes different; small prominence at border of left helix; feet flat; mammary glands small, left bigger, papillae inverted; scoliosis of highest degree of dorsal part of column; cremasteric reflex absent on both sides; dermographia absent; atrophy of left hypothenar and left supraspinatus muscle
3 G. C. ♀ 14	Irises green-gray with incomplete brown circle and numerous brown spots differently distributed in the two eyes; in periphery of right iris, several white spots	Microcephaly; forehead high; glabella broad, prominent; metopism	Imbecile level	Lower part of sternum depressed; winged and scaphoid scapulas; left papilla fissured; left areola less dark; slight atrophy of right infraspinatus and both supraspinatus muscles; a few hairs at sacrum; right fifth finger deformed; second toe bigger than other toes on both feet; periosteal reflex of both arms absent

Case No., Name, Sex, Age (Years)	Eyes	Clinical Features	Diagnosis	Comment
4 W. G. ♀ 28	Irises gray; in right, a few reddish brown lines in right upper quadrant	Microcephaly; forehead bulging in midline; glabella broad; synophrys; frontal suture slightly bulging; upper lip and cheeks hairy; root of nose depressed	Moron level	Obesity of buttocks, abdominal wall and thighs; face free; mammary glands different, poorly developed, with abnormal hairs above areolas; lanugo at sacrum; syndactyly, both feet; cremasteric reflex absent on both sides
5 P. E. ♀ 24	Right iris more brown; left grayish brown; scleras bluish	Caput quadratum; glabella very broad; metopism	Athetosis; moron level	Ear lobes different in shape; mammary glands different, left larger, with bigger areola and more prominent papilla; scoliosis of dorsal portion of column; both feet extremely flat; atrophy of hypothenar and fourth interosseus dorsalis muscle on both sides; inferior abdominal and cremasteric reflexes absent on both sides; dermographic response absent; lanugo on right thigh; black hairs on left
6 N. L. ♂ 13	Right iris brown; left gray	Forehead high, bulging; glabella rather broad; congenital dislocation of both hips; right eye slanting; metopism	Epilepsy	Ear lobes different, very short; lanugo all over backside; many brown moles on both legs; both lower extremities thin; pes calcaneus, both feet; shape of fifth fingers irregular
7 D. L. ♂ 12	Right iris gray; left grayish with brown spots and brown circle; paralysis of right abducens nerve	High skull with bulging frontal bosses, broad glabella and depressed root of nose; metopism; chin strong, broad, with deep groove	Epilepsy; injury at birth	Antithenar and supraspinatus and fourth interosseus dorsalis muscle (of hand) on both sides weak; both fourth toes deformed; right big toe covered by second toe; few hairs at sacrum; small joints of fingers and toes lax; patient dumb
8 R. W. ♂ 26	Irises bluish gray; in right, a few brown spots; palpebral fissures narrow	Turricephaly with broad, bulging glabella; metopism in lower part of forehead; root of nose depressed; synophrys; occiput flat; epicanthal folds on both eyes	Cretinism	No terminal hair; pubic hair scanty, "horizontal"; sternum depressed; Recklinghausen's spots and neurofibromas scattered; fat deposits at thighs and buttocks; Meyer reflex on left side and lower abdominal reflex on both sides absent; scrotal reflex present
9 R. W. ♀ 18	Irises grayish green; in right, scattered brown spots	Flattening of head over left temporal and parietal region; root of nose slightly depressed; glabella broad; metopism	Imbecile level	Pubic hair of virile type; breasts different in size; lanugo at sacrum; lower part of both legs hairy; cremasteric and triceps reflexes absent on both sides

Case No., Name, Sex, Age (Years)	Eyes	Clinical Features	Diagnosis	Comment
10 L. L. ♀ 15	Irises blue; left light blue; right more grayish blue; left, high myopia (— 20 D. sph.), large white patch and pigment changes below disk; right, large white atrophic patch, including entire maculary region, high myopia (— 20 D. sph.)	Hydrocephalus with prominent frontal bosses, slightly depressed root of nose, broad glabella; metopism	Hydrocephalus; epilepsy; spastic tetraplegia	Ear lobes different, with big lobules; bilateral equinovarus of highest degree; atrophy of both legs with isodactyly and paraplegia; bilateral Rossolimo and Mendel reflexes; spastic paraplegia of both arms; lower abdominal and cremasteric reflexes absent on both sides; incontinence; obstinate constipation; mammary glands different in size; lumbar lordosis absent
11 H. B. ♂ 16	Right iris blue; left, blue-gray	Microcephaly with high skull; glabella flat, rather broad; root of nose slightly depressed; metopism; chin high, strong	Microcephaly; idiot level; injury at birth	Extremely short, adherent lobules; papillae different; left middle finger irregular in shape; right middle toe laterally deviated; lanugo at lower part of back; no terminal hairs; pubic hair "horizontal"; incontinence; feet very flat; Recklinghausen-like spots scattered; difficult instrumental delivery
12 S. W. ♂ 9	Right iris brown; left bluish white; congenital microphthalmia on left; defect of right macula	Hydrocephalus with high skull; ridge in midline of frontal bone; glabella broad; chin high; tip of nose snub; marked symmetric dilatation of ventricular system and excessive amount of air over periphery	Hydrocephalus; idiot level	Difficult delivery; strong lanugo at backside; atrophy on both sides of infraspinatus, supraspinatus and deltoid muscles; periosteal, triceps and Meyer reflexes missing on both sides
13 B. B. ♀ 8	Right iris grayish blue with white spots in periphery; in left iris, an ill defined area in inner lower quadrant whitish	Choreatic movements of all limbs	Chorea; congenital syphilis; imbecile level	Glabella very wide; metopism; chin high, comparatively strong; delicate veins at forehead; mole in lumbar area; Wassermann reaction of mother positive during pregnancy
14 E. A. ♂ 11	Irises gray; in upper half of left, several brown spots	Twitching of both sides of face; tendency to spasticity (flexion) of both hips, elbows and knees; inability to walk or stand up	Little's disease; facial tic; moron level	High forehead; glabella very broad; chin rather receding; facies birdlike; occipital region flattened, parietal depressed; metopism to the right; patient prematurely born at 7 months; cyanotic when born
15 J. H. ♀ 5	Irises gray; in right, a large brown sector in upper lateral part; in left, a brown circle close to pupil	Active motion of both legs limited; contracture of both elbows; stiffness to some extent of both shoulder joints; marked enlargement of lateral and third ventricle; unusually large amount of air over periphery; thin shell of cortical substance between ventricles and peripheral space; peripheral atrophy most marked in frontal area	Cortical atrophy of brain; microcephaly; idiot level	Patient born about 3 weeks prematurely; labor lasted 14 hours; glabella broad; temples sunken; metopism; occiput protruding; chin strong; abdominal muscles extremely weak; evenly distributed atrophy of all extremities

All the cases of this group were cases of heterochromia simplex according to the classification of E. Fuchs, except case 10, in which heterochromia was combined

with myopic chorioiditis, and case 12, in which there were heterochromia plus severe congenital abnormalities in both eyes. The patients showed, aside from their brain lesions, some interesting structural abnormalities and cannot, consequently, be considered as normal. Under the heading "Comment" the most striking signs are briefly summarized.

As to case 1, the lanugo at the sacral area, the midsternal depression and, according to my [8] investigations, the absence of the cremasteric reflex on both sides and the peculiar type of obesity are among the signs of status dysraphicus, that is to say, of an abnormal development of the spinal cord in its lumbar segment. Evidence of any abnormality in the cervical or the dorsal segment could not be found. The microcephaly and the idiocy of mongolian type are noteworthy.

In case 2, the atrophy of the left hypothenar and supraspinatus muscle might be accounted for by a spinal lesion at the level of the fifth and sixth cervical and the seventh and eighth cervical and first thoracic segments, respectively; that is, in an area close to Budge's center, since signs of peripheral neuritis were lacking. A difference in the size of the mammary glands, abnormal papillae and a high degree of flatness of the feet and of scoliosis are signs of the status dysraphicus.[9] Therefore in this case a lesion of both the upper and the lower part of the spinal cord was suggested.

In case 3, status dysraphicus was probably present, on account of the deformity of the fifth finger of the right hand, the depression of the sternum, the difference in the papillae and areolas, the abnormal length of the second toe on both feet and the hairiness of the sacrum. The slight atrophy of the right infraspinatus and both supraspinatus muscles pointed to a lesion of the fifth and sixth cervical segments, as peripheral neuritis could be ruled out. The absence of a radial reflex could be traced to a lesion of the seventh and eighth cervical segments.

In case 4, status dysraphicus was evidenced by lanugo at the sacrum, syndactyly, absence of the cremasteric reflex on both sides and the difference in the mammary glands.

In case 5, the atrophy of the hypothenar and of the fourth interosseus dorsalis muscles of the hands might be explained by a lesion at the level of the eighth cervical and first thoracic segments. The dorsal scoliosis of high degree and the extreme flatness of both feet may also have been connected with a spinal involvement. The difference in the size of the mammary glands, the absence of the cremasteric reflex on both sides, and the lanugo confined to one thigh were signs of dysraphia.

In case 6, the irregularity of the fifth finger of both hands, the atrophy of both legs and the absence of both the knee and the ankle reflexes were probably due to a lesion of the anterior horns.

In case 7, there was probably damage to the lowest cervical and to the lumbar segment.

In case 8, the impairment of the genital function, the absence of the lower abdominal reflex on both sides and the absence of the Meyer reflex on the left side may have been due to a lesion of the pyramidal tracts; the scrotal reflex might be explained by an incomplete interruption of the pathways above the level of the second lumbar segment.

In case 9, the sacral lanugo, the absence of the cremasteric reflex on both sides and the difference in the size of the breasts were consistent with the suggestion of status dysraphicus (in the lumbar segment). The virile type of pubic hair and the hairs on the lower legs constituted hirsutism. I am dealing with this problem in another article.

8. Hess, L.: J. Nerv. & Ment. Dis., to be published.
9. Henneberg, R., and Koch, M.: Monatschr. f. Psychiat. u. Neurol. **54**:117, 1923.

Case 10 presented a complicated problem. There was heterochromia plus myopic choroiditis and damage to the brain (hydrocephalus, epilepsy). The obstinate constipation along with the incontinence of the urinary bladder and the absence of cremasteric reflexes might be accounted for by an involvement of the gray substance of the spinal cord (lumbar area). The atrophy of both legs (of high degree) could be explained by a lesion of the anterior horn cells at the same level. Isodactyly and a difference in size of the mammary glands belong to dysraphia. From the clinical standpoint there was at first glance some similarity to Pelizaeus-Merzbacher disease or to amaurotic idiocy (Sachs-Tay). The condition could be differentiated from the latter by the changes in the eyegrounds and from the former by the lack of a hereditary tendency, by the sex of the patient and by the changes in the eyegrounds.

In case 11, the microcephaly and idiocy were probably a result of damage to the spinal cord due to injury at birth.

In case 12 in addition to hydrocephalus, there was damage to the lower cervical portion of the spine.

In case 13, there were congenital syphilis and chorea due to damage to the brain.

In case 14, there was diffuse damage to the brain (so-called Little's disease).

In case 15, there were cortical, mostly frontal, atrophy and hydrocephalus.

The signs referable to the spine in the cases of this group belong to status dysraphicus, i.e., lack of closure of the primary neural tube (Henneberg and Koch [9]). The clinical signs of this congenital abnormality according to Bremer [10] are a high-arched palate, funnel chest or other anomaly of the sternum, kyphoscoliosis, winged scapula, a difference in shape and size of the mammary glands, irregularities in the shape of the fingers increasing toward the ulnar side, webbed toes, enuresis, abnormalities of the reflexes of the upper extremities, etc. Passow,[11] on the other hand, in his important paper stated that heterochromia simplex (Fuchs) as well as the acquired types of heterochromia (those which occur after lesions to the sympathetic trunk and to the spinal cord) have no relationship to dysraphia. My findings, in contradistinction to those of Passow, corroborate the conclusion that heterochromia simplex (Fuchs) is not a local but rather a deeply rooted, more generalized, congenital condition involving, aside from the eyes, either the spinal cord or the brain or both. In a later section I shall try to give an explanation on a broader basis.

II. HETEROCHROMIA COMPLICATA

The following 2 cases are instances of heterochromia complicata, that term being given a broader sense than that in which Fuchs used it.

Case No., Name, Sex, Age (Years)	Eyes	Clinical Features	Diagnosis	Comment
16 D. C. ♂ 18	Irises gray, right lighter with central brown ring and few brown spots, from pinpoint to double pinpoint size; hyperopia of both eyes (2.00 D. sph.); retinitis pigmentosa (syphilitic chorioretinitis?)	Obesity; "horizontal," scanty pubic hair; gynecomastia; metopism; chin rather strong	Moron level	Skull and forehead high; glabella not large; larynx not strong, hardly palpable; few blond hairs at level of iliac crests; axilla hairless; no terminal hair; marked cubitus valgus; lanugo at buttocks and anal cleft; racemose livedo all over body; deformity of both fifth fingers; toes irregular in size; big toe very thick; cremasteric reflex absent on both sides; one sister epileptic with no retinal changes; parents not related

10. Bremer, F. W.: Deutsche Ztschr. f. Nervenh. **95**:1, 1926; **99**:104, 1927.
11. Passow, A.: Arch. f. Augenh. **107**:1, 1933.

Case No., Name, Sex, Age (Years)	Eyes	Clinical Features	Diagnosis	Comment
17 C. F. ♀ 8	Right, greenish brown; left, lighter, with several ill defined brown spots; large coloboma of left retina; border of left disk rather diffuse	Bifid uvula; partially cleft palate; notched, irregular teeth; paresis of right leg with increased knee and ankle jerks; enlarged lateral ventricles and considerable air over periphery	Hydrocephalus; right hemiplegia; epilepsy; idiot level	Asymmetry of face; metopism, with bulging; glabella very broad; forehead broad; occiput flat (acrobrachycephaly); chin not unusual; some lanugo at sacrum; fifth metatarsophalangeal joint on both feet abnormally located; abdominal and cremasteric reflexes absent on both sides; incontinence; patient does not talk; frequent epileptic convulsions

In case 16, the outstanding feature was the endocrine disorder (obesity, lack of terminal hair, gynecomastia and a feminine appearance), which was similar to Fröhlich's syndrome. The signs of status dysraphicus were not well developed, although some of them could be detected (lanugo at the anus, deformity of the fifth fingers, irregularity in the size of the toes and absence of the cremasteric reflex). I shall speak of the glabella later on.

In case 17, the signs of dysraphia (sacral lanugo, abnormal insertion of both fifth toes, absence of the cremasteric reflex and incontinence) were noteworthy, as were the cerebral signs (hydrocephalus, disclosed by an encephalogram, and right hemiplegia). Signs of localized atrophy were not present.

In both these cases the term heterochromia complicata was used because of severe congenital anomalies in the eyegrounds in addition to the heterochromia. Cases 10 and 12 could well have been listed in this group.

III. HETEROCHROMIA SYMPATHICA

The following tabulation presents in brief form a report on a case of heterochromia in association with Horner's syndrome (heterochromia sympathica, subtype 1):

Case No., Name, Sex, Age (Years)	Eyes	Clinical features	Diagnosis	Comment
18 L. V. ♂ 25	Left iris light gray-brown with few brown spots; right iris green with brown circle close to pupil and brown radii; left palpebral fissure and pupil markedly smaller; enophthalmos on left; tic of left upper lid; eyegrounds normal; glabella prominent, broad	Spasticity and atrophy of left arm and leg; pes cavus on left	Left hemiathetosis; idiot level	Atrophy of left trapezius, supraspinatus and infraspinatus muscles; left costal arch higher up than right; left mamilla much more hairy than right; ear lobes different; lumbar lordosis absent; lumbosacral area down from level of iliac crest hairy; incontinence; cremasteric reflex absent on both sides; prominence in midline of forehead; instrumental delivery

The findings in this case suggest (1) diffuse damage to the brain, (2) cerebral hemorrhage, during delivery, to the right motor area, extending to the basal ganglions of the same side, and (3) spinal hemorrhage from the level of the third cervical to the eleventh thoracic segment, the trapezius muscle being innervated by the accessorius nerve and the ventral rami of the third and fourth cervical nerves, and the supraspinatus and the infraspinatus muscle by the suprascapular nerve (from the fifth and sixth cervical nerves), the ciliospinal center being located

at the first thoracic segment. It should be mentioned that both pupils reacted normally to light and to distant vision, the dilation in response to pain being slightly less than normal. The prominence of the forehead was apparently similar to the prominence of Crouzon's [12] craniofacial dysostosis. I shall return to this fact in the section on etiology.

ETIOLOGY

The explanation of heterochromia would be more satisfactory if it accounted for all types of the anomaly, for heterochromia simplex as well as for heterochromia complicata and sympathica.

Some authors have suggested a hereditary factor, the color of the one iris being inherited from one parent and the color of the other iris from the other parent (*Mosaikvererbung*). Modern investigators, for example Goldschmidt, one of the foremost experts in the field of heredity, however, have denied the occurrence of this kind of inheritance, at least in experimental animals. Other authors have focused their attention on an involvement of the sympathetic trunk, suggesting a disturbance of sympathetic influence as the main underlying cause of heterochromia.

A definite lesion of the cervical portion of the sympathetic trunk has been familiar since Bernard and Horner described independently their well known syndrome. In cases of sympathetic nerve lesions with the Bernard-Horner syndrome, heterochromia is strikingly rare. Surprisingly rare, in my opinion, is the occurrence of heterochromia after surgical intervention on the sympathetic trunk. Finally, in my second subclassification of heterochromia sympathica, in addition to the heterochromia, other organic lesions, particularly anomalies in the structure of the eyeball (ectopy of the pupil, juvenile cataract, coloboma, persistent pupillary membrane, etc.) are encountered, demonstrating that a deeper, embryologic disturbance is to be kept in mind.

In the second type according to Fuchs (heterochromia complicata), neither the hypothetic *Mosaikvererbung* nor an involvement of the sympathetic system would provide a satisfying explanation.

From a broader point of view, three factors, according to my experience, are outstanding in congenital heterochromia: I. An involvement either of the spinal cord or of the brain or of both. II. A characteristic type of skull. III. Prevalence of a particular type of complexion.

I. INVOLVEMENT OF SPINAL CORD

The involvement of the spinal cord may be considered as belonging to status dysraphicus [9] on account of the various clinical signs mentioned under the heading "Comment" in the case reports. It is, however, possible to go deeper into the matter and to attempt to give a more precise definition of the site of the spinal lesions. This attempt is based on (1) signs of localized muscular atrophy, (2) reflex abnormalities, (3) vasomotor changes, (4) disturbance of the function of the urinary bladder and of the bowels, (5) abnormalities in the distribution of the fat and (6) scoliosis of the spine.

1. *Muscular Atrophy.*—Localized atrophy could be demonstrated in cases 2, 3, 5, 6, 7, 12 and 18. On palpation neither pain nor tenderness could be elicited. One should, however, not forget that in view of the mental condition of the patients, exact testing was sometimes not possible. It is well to note that the involved gray matter in the cases reported, the cervical enlargement, was located in the vicinity of Budge's center, a sympathetic center of pupillary motility. The equally dis-

12. Crouzon, O.: Etudes sur les maladies familiales nerveuses et dystrophiques, Paris, Masson & Cie, 1929.

tributed atrophy of both legs, the hirsutism localized over the sacrum, the syndactyly and the abnormalities of the cremasteric and abdominal reflexes (cases 4 and 6) point, on the other hand, to an involvement of the lumbar enlargement. The lesion of the spinal cord I have in mind is a congenital and apparently a nonprogressive one and differs in these respects from the lesions in syringomyelia and progressive muscular dystrophy. As for the latter disease, it is surprising that some of the muscles frequently involved (for example the deltoid, supraspinatus and infraspinatus) are also the site of atrophy in cases of heterochromia. Many years ago Bing [13] called attention to the fact that the localization of congenital muscular defects and of progressive muscular dystrophy are about the same.

2. *Reflex Abnormalities.*—The cremasteric reflex was absent on both sides in cases 1, 2, 4, 9 and 16; the cremasteric and abdominal reflexes were absent in cases 5, 8, 10 and 17; the triceps reflex was absent in case 9; the periosteal reflex of the upper extremities was absent in case 3; the triceps, periosteal and Meyer reflexes were absent in case 12, and a scrotal reflex was noticed in case 8.

According to the modern concept the center of the radial reflex may be localized to the seventh and eighth cervical segments, the triceps reflex to the sixth and seventh cervical segments and the cremasteric reflex to the first and second lumbar segments.

The Meyer reflex is important for the diagnosis of lesions of the pyramidal tract. It is abolished, according to almost all modern authors, in every case in which the cerebrospinal pathway is interrupted. The findings in the cases reported are consistent with organic lesions in the gray matter of the cervical or lumbar enlargement (localized atrophies combined with abolition of certain reflexes).

3. *Vasomotor Changes.*—It is beyond the scope of this paper to discuss at length the vasomotor abnormalities frequently encountered, such as coolness of the hands, slight cyanotic discoloration of both arms and legs and a tendency to cyanosis of the finger tips. It is enough to remember that a vasomotor center for the upper extremities is likely to be located at the upper and the middle part of the spinal cord.

4. *Incontinence.*—The question of incontinence of the bladder is complicated. One is entitled to assume the existence of a sympathetic center in the lateral horn of the lowest thoracic and the uppermost lumbar segment and at the same level a motor center of the bowels (obstinate constipation in case 10).

5. *Distribution of Fat.*—This depends largely on nervous (spinal and cerebral) factors. I am dealing with this problem in a special paper. Suffice it to say that the unusual distribution of fat in cases 1, 4 and 8 was due to a spinal factor.

6. *Scoliosis of the Spine.*—It should be briefly mentioned that in cases of severe scoliosis anatomic lesions in the lateral horn cells may be found. Scoliosis was severe in cases 2 and 5.[14]

Conclusions.—From the foregoing discussion one may conclude that in some of the cases of congenital heterochromia reported (heterochromia simplex, sympathica and complicata) there were objective signs of spinal damage, in the cervical or the lumbar area, belonging in a broader sense to the status dysraphicus. Neither the heterochromia nor the spinal damage is incidental, but they may be accounted for by a congenital anomaly of the spinal cord. The site of this anomaly may be placed at the level of the cervical enlargement, at least in some cases. In other instances an involvement of the brain can be assumed (mongolism and microcephaly,

13. Bing, R.: Virchows Arch. f. path. Anat. **170**:175, 1902.

14. It may be noteworthy that in many cases of Friedreich's disease, a congenital abnormality of the cerebrospinal system, scoliosis, of some degree is present.

case 1; athetosis and epilepsy, case 2; athetosis, case 5; epilepsy, case 6; spastic tetraplegia, case 10; hydrocephalus, case 12; chorea, case 13; Little's disease and tic, case 14, and cortical atrophy, case 15). Aside from damage to the brain, spinal damage could be demonstrated, as indicated by the findings listed under "Comment" in the case reports.

II. STRUCTURE OF SKULL

While studying patients with heterochromia, I was impressed with the appearance of the skull. Since in the literature on congenital heterochromia the skull has never been given special attention, it would seem to be of interest to describe briefly the main features.

The head is brachycephalic or mesocephalic. The forehead, in many but not in all cases bulging in its upper part, with pronounced frontal bosses, shows a definite metopism. This metopism, which begins immediately above the glabella either is located in the midline or deviates to the right or to the left, apparently according to a concomitant asymmetry of the skull. It extends rarely from the nasion up to the bregma; mostly it is confined to the frontal suture and must be searched for. In some instances the uppermost part of the frontal suture was not open but was somewhat prominent, resembling the suture in so-called craniofacial dysostosis (Crouzon [12]). I shall mention this condition later on. Consistent with the asymmetric metopism is the fact that the face appeared to be asymmetric, the zygomatic arches, the angles of the mouth and the nasolabial folds being decidedly different.

Moderate bulging of the frontal eminences is not unusual in the skulls of children and of females and should not be stressed, whereas metopism itself or metopism in conjunction with asymmetry of face and forehead is worth mentioning. In the newborn child, the two halves of the frontal bone are separated by the anterior acute angle of the anterior fontanel, but within the second year the anterior fontanel as well as the frontal suture becomes closed. The closure of the latter takes place, not by primary ossification, but by means of a secondarily intercalated mass (supranasal triangle). As the asymmetry of the skull and the failure of the frontal suture to close are indicative of an abnormal development of the skull, it seems to be noteworthy that in the children reported on the glabella (according to modern anthropology the space between the two superciliary ridges) is slightly depressed and strikingly broad. The width of the glabella is determined by the pars nasalis of the frontal bone. The development of the frontal bone, in turn, is largely dependent on the growth of the frontal lobe. The metopism and the width of the glabella in my opinion are both connected with an abnormal growth of the skull and of the forebrain.

The eyebrows of the patients under discussion were present and were separated, but there was a rare tendency to fuse (cases 1, 4 and 8).

The width of the mandible is dominated by the distance between the two fossae articulares at the base of the skull. The body of the mandible, particularly the middle part and the chin, was in general well developed. There was a receding chin in case 14.

The prominence of the uppermost part of the forehead in some of the patients reminds one of Crouzon's [12] craniofacial dysostosis. The classic picture of this disease is characterized by central prominence of the forehead, prognathism, exophthalmos, external squint and a peculiar beaklike nose, all of which signs were absent in the cases reported. It might be of greater importance to call attention to ocular hypertelorism, described by Grieg,[15] the outstanding feature of which is the excessive distance between the two eyeballs, as in the cases under discussion.

15. Grieg, D. M.: Edinburgh M. J. **31**:560, 1924.

Furthermore, there is a marked vertical groove in the forehead, extending upward from the root of the nose. The bridge of the nose is broad or, sometimes, flattened. The orbits are divergent, and an external squint may be present. The occiput is flat, the temporal regions both bulging. Although some of these signs could not be detected in the patients reported on, a mild form of, or a certain relationship to, hypertelorism might be considered. As far as metopism and heterochromia are concerned, Grieg did not mention these signs as being associated with hypertelorism.

The widening of the interorbital space along with metopism is known in anthropology as euryopia. Its relationship to heterochromia has not been noticed in the literature.

III. COMPLEXION

Among 21 patients with congenital heterochromia, one had fair blond, one dark red and the remainder dark blond or dark brown hair. As to red hair, the problem is not yet settled from the anthropologic point of view. I am, however, more inclined for many reasons to believe that dark red hair may go with a dark complexion. The prevalence of a dark complexion among children with heterochromia of the iris would then be evident. Among 15 persons with heterochromia aged between 60 and 80 whom I examined, nearly the same prevalence of a dark complexion was observed. Further studies of this aspect are necessary, however, in which the proportion of fair blond and of dark-haired persons in the entire white population will be taken into consideration.

The coincidence of congenital heterochromia with the signs of status dysraphicus, the characteristic structure of the skull and, finally, the dark complexion are interesting. Granted that the signs of dysraphia are delicate and need careful search, they are demonstrable in any case of heterochromia. The association is not incidental, as one might suggest, since most of the studies have been carried out in a state school, whose inmates present many congenital anomalies. The regularity of the changes, confined to a special area of the spinal cord, is not in favor of such a suggestion. However, in order to avoid a mistake, it was necessary to corroborate my statements in every possible way. About 450 children, ranging from 3 to 18 years of age, suffering from various diseases of the nervous system (congenital hemiplegia, chorea, athetosis, rigidity, hydrocephalus, disseminated sclerosis, Friedreich's disease, adiposogenital dystrophy, tuberosclerosis), but isochromic, were carefully studied. The result was negative as far as the coincidence mentioned is concerned. Within the last two years, more than 400 persons between 60 and 80 were examined in a home for the aged. It was striking that of a group of 15 with heterochromia, signs of dysraphia were present in all. The skull of an aged person undergoes many changes, becoming shorter and broader (senile chameprosopia). It cannot be compared to the skull of a child. The prevalence of a dark complexion was mentioned. A decision with respect to the complexion cannot yet be reached.

SUMMARY

1. Patients with congenital heterochromia of any type (the types were defined in the first section of the paper) present signs of status dysraphicus and a characteristic structure of the skull. As for the complexion, further investigations are necessary.

2. Heterochromia is not a localized peculiarity of the iris but is connected with an abnormal development of the skull, the spinal cord and the brain.

3. Heterochromia and many of the nervous signs can be accounted for by a congenital anomaly of the lowest part of the cervical portion of the spinal cord.

15 Kenwood Street.

INTRAOCULAR HEMORRHAGES IN CHOLINE DEFICIENCY

JOHN G. BELLOWS, PH.D., M.D.
AND
HERMAN CHINN, PH.D.
CHICAGO

Recently it has been demonstrated that serious changes can be produced within two weeks when weanling rats are placed on choline-poor diets.[1] Hemorrhagic kidneys and adrenals, fatty liver, enlarged spleen and atrophied thymus are the most consistent findings. In addition, hemorrhages are frequently found in the lungs, myocardium, lymph nodes and eyes.[2] The mention of ocular hemorrhages drew our attention to the possible ophthalmologic implications.

Choline (trimethylhydroxyethylammonium hydroxide) is a moderately strong base occurring as a part of the lecithin in bile, brain, egg yolk, etc. Morgan [3] called it a water-soluble vitamin. It is directly active lipotropically; i. e., it prevents development of fatty liver or accelerates the disappearance of abnormal fat from the liver [4] and is concerned more indirectly in carbohydrate metabolism.[5] It appears likely that choline may be involved in the metabolism of cholesterol as well as in that of neutral fat.[6] It has been found to prevent hemorrhagic kidney in rats.[1] In chicks, choline prevents perosis [7] and acts as a growth essential. Maclean, Ridout and Best [7] have demonstrated that the fatty changes in the liver cause a decrease in the storage of glycogen and a decrease in the excretion of bromsulphalein. Cholesterol and cystine aggravate while methionine and a high protein diet ameliorate the hepatic damage produced by a deficiency of choline.[8] The hemorrhagic degeneration so noticeable in the kidney occurs most readily in actively growing young animals and requires a diet almost absolutely free from choline, for even if only one-half the amount of choline required to prevent fatty liver is present in the diet hemorrhagic changes do not occur. Griffith and Mulford [8b] have demonstrated that the ordinary antihemorrhagic factors, such as vitamin K, vitamin C and vitamin P, do not influence the hemorrhagic condition caused by choline deficiency.

EXPERIMENTS

Weanling rats 21 to 28 days old were kept in individual cages with raised screen floors. A modified Engel and Salmon diet [2] was fed ad libitum:

	Per Cent
Peanut meal (extracted)	30
Casein (extracted)	6
Lard	6
Salt mixture (Osborne and Mendel)	4
Sucrose	53.7
Cystine	0.3

From the Department of Ophthalmology, Northwestern University Medical School.

1. Griffith, W. H., and Wade, N. J.: J. Biol. Chem. **131**:567, 1939.
2. Engel, R. W., and Salmon, W. D.: J. Nutrition **22**:109, 1941. Griffith.[1]
3. Morgan, A. F., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 10, p. 369.
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5. Jukes, T. H.: J. Nutrition **20**:445, 1940.
6. Best, C. H.: Science **94**:523, 1941.
7. Maclean, D. D.; Ridout, J. H., and Best, C. H.: Brit. J. Exper. Path. **18**:345, 1937.
8. (*a*) Griffith, W. H.: J. Nutrition **21**:291, 1941. (*b*) Griffith, W. H., and Mulford, D. J.: ibid. **21**:633, 1941.

One drop of percomorph liver oil was added for every 100 Gm. of diet. The diet was further enriched by the following crystalline vitamin mixture:

Thiamine hydrochloride, riboflavin, pyridoxine hydrochloride and calcium pentothenate, 85 mg. each per kilogram of diet; menadione (2-methyl-1, 4-naphthoquinone), 5 mg. per kilogram; nicotinic acid and niositol, 1 Gm. per kilogram each, and paraaminobenzoic acid, 3.5 Gm. per kilogram.[9]

This mixture provided a diet low in methionine and choline, high in cystine and low in fat. In rats fed this diet a typical choline deficiency consistently developed within five to fourteen days. Control animals received 5 to 25 mg. of choline chloride daily. Modifications of the basic choline-poor diet provided (1) a diet low in choline and methionine, high in fat and high in cystine; (2) a diet low in choline and methionine, high in fat and low in cystine (low cystine diet); (3) a diet low in choline and methionine, high in fat and cystine and enriched with cholesterol, and (4) a diet low in choline and methionine, high in fat and cystine and low in vitamin B complex. Since the ocular effects observed in animals fed the modified diets did not differ significantly from those in animals fed the basic choline-poor diet, details of the composition are omitted. Examinations of the blood and of the eyes were made daily. The rats were killed when hemorrhages were maximal. The eyeballs were removed, sectioned and stained with hematoxylin and eosin or with sudan III.

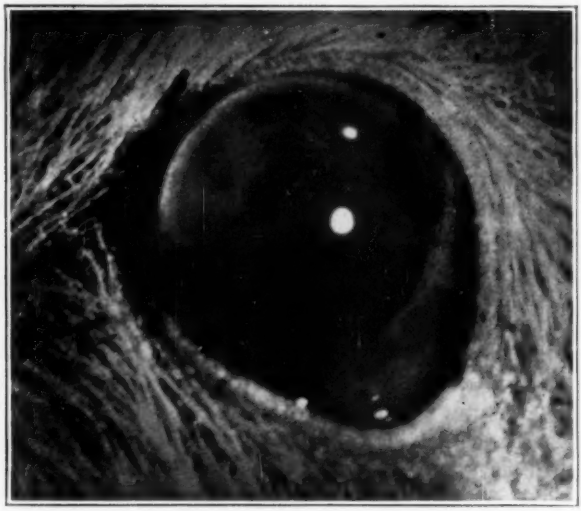

Fig. 1.—Hyphemia.

RESULTS

As in the work of Griffith and Wade and of other workers, nearly all the rats on a choline-poor diet failed to gain the normal amount of weight. Many died before the end of the week, but those surviving the acute phase made a rapid recovery. The bleeding time of nearly all was greatly prolonged. The prothrombin time was frequently increased, but the results were too erratic to justify any definite conclusions. A marked decrease in the platelet count, occasionally observed, requires further investigation. Many rats showed a blood-specked nose, hemorrhage into the nail beds and bloody tears. In each litter of 6 to 10 animals, 1 or 2 (a total of 22 animals) showed some type of intraocular hemorrhage, usually within the forty-eight hours before death. The most frequent form was a column of blood in Cloquets' canal; next in frequency was a hemorrhage apparently arising in the region of the ciliary body and shortly spreading beyond the crystalline lens;

9. These preparations as well as cystine and methionine were furnished by Merck & Company, Inc.

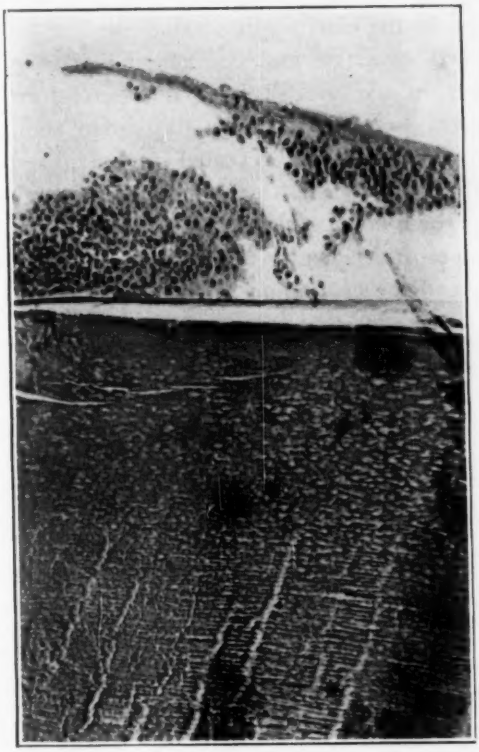

Fig. 2.—Free blood between the anterior limiting membrane of the vitreous and the crystalline lens.

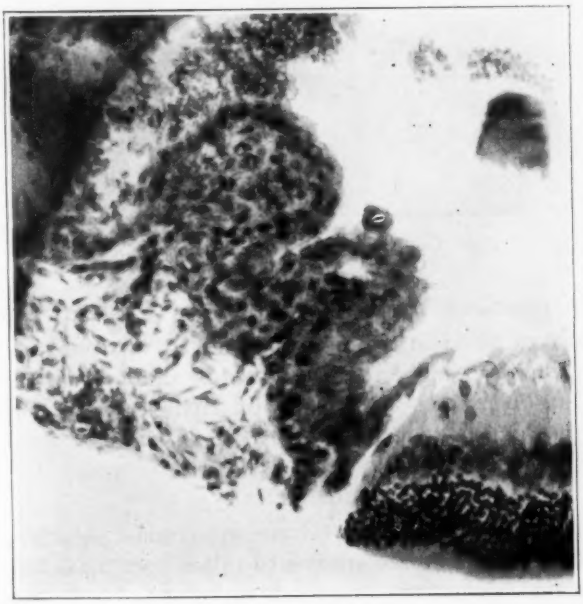

Fig. 3.—Swelling and hemorrhage of the ciliary processes.

less commonly, hemorrhages visible to the naked eye appeared as hyphemia (fig. 1). The pathologic changes in the kidneys, liver, lungs and other organs are adequately described in the reports of Engel and Salmon and of other writers. However, the histologic changes in the eyeball have not heretofore been reported. No pathologic fatty changes were disclosed by the sudan stain. However, sections stained with hematoxylin and eosin revealed a generalized engorgement of the vessels throughout the eyeball. The three forms of hemorrhages observed during life were paralleled by the following observations:

1. Free blood was most frequently found between the anterior limiting membrane of the vitreous and the crystalline lens (fig. 2).

Fig. 4.—Blood in the anterior chamber.

2. The ciliary processes (fig. 3) were swollen and frequently hemorrhagic.

3. The presence of blood in the anterior chamber was not uncommon (fig. 4).

To determine whether a higher animal would be similarly affected, puppies were placed on a choline-free diet. While hepatic changes were noted, hemorrhagic degeneration in the kidneys, eyes and other organs did not occur.

COMMENT

Whether the findings disclosed here have any clinical significance is unknown. Although superficial similarities are apparent (1) between the enlarged hemorrhagic kidney with associated ocular hemorrhages in animals and hypertensive retinopathy in man and (2) between the fatty liver with decreased ability to store glycogen in animals (resembling the condition in depancreatized dogs) and diabetic retin-

opathy in man, one must not hastily conclude that choline plays a role in these diseases in man. The presence of lecithin in so many articles of the normal diet makes it unlikely that a choline deficiency on a purely dietary basis exists in man. However, some conditions of ophthalmologic interest in which a possible deficiency may arise are pernicious anemia and diabetes mellitus. In these diseases there is a marked tendency to fatty changes in the liver, and the demand for choline is probably greater than normal.

Dr. S. R. Gifford gave advice on this work.

720 North Michigan Avenue.

Ophthalmologic Reviews

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BACTERIOLOGIC OBSERVATIONS ON INFECTIONS OF THE EYE

CHARLES WEISS, M.D., PH.D.
SAN FRANCISCO

OUTLINE

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XIII. Virus infections of the eye

I. INTRODUCTION

With the development in recent years of a variety of sulfonamide compounds [1] and specific bactericidal and antitoxic serums [2] for the treatment of infections of the eye, the etiologic diagnosis of diseases of the conjunctiva and cornea has become an essential and practical procedure. This is especially true because there are no constant or absolutely typical clinical pictures corresponding to individual infections with the exception of those due to Spirochaeta pallida, Malleomyces mallei,

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From the Clinical and Research Laboratories of the Mount Zion Hospital.

1. For literature on the use of the sulfonamide compounds in the treatment of ophthalmic infections, see: (*a*) Bruens, E.: Zur Chemotherapie der Gonoblennorrhoe der Neugeborenen, Klin. Monatsbl. f. Augenh. **105**:430, 1940. (*b*) Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, Arch. Ophth. **27**:34 (Jan.) 1942. (*c*) Glover, L. P.: Some Uses of Sulfanilamide in Ophthalmology, Am. J. Ophth. **22**:180, 1939. (*d*) Guyton, J. S.: Effects of Sulfanilamide and Sulfapyridine on the Koch-Weeks Bacillus (Haemophilus Influenzae), Arch. Ophth. **23**:1243 (June) 1940. (*e*) Guyton, J. S.: Local Use of Sulfanilamide Compounds in Eye, Am. J. Ophth. **24**:292, 1941. (*f*) Jones, C. C.: The Use of Sulfanilamide in Otolaryngology and Ophthalmology, Iowa State M. J. **29**:6, 1939. (*g*) Landegger, G. P.: Sulfanilamide in Ophthalmology, California & West. Med. **55**:200, 1941. (*h*) Luo, T. H., and P'an, S. Y.: Concentration of Sulfanilamide in the Aqueous Humor of Human Eyes, Chinese M. J. **58**:167, 1940. (*i*) MacCallan, A. F.: Sulfonamide Treatment of Bacterial and Trachomatous Conjunctivitis, Brit. M. J. **1**:482, 1940. (*j*) Miller, J.: Sulfapyridine in Pneumococcus XIX Ophthalmia, New York State J. Med. **40**:1389, 1940. (*k*) Mullen, C. R.: Sulfathiazole for Gonorrheal Eye Diseases, Am. J. Ophth. **25**:59, 1942. (*l*) Panneton, P.: Local Treatment of Gonorrheal Conjunctivitis with Sulfanilamide Powder, ibid. **24**:314, 1941. (*m*) Thygeson, P.: Sulfanilamide Therapy of Inclusion Conjunctivitis, ibid. **22**:179, 1939.

2. Scheie, H. G., and Collins, L. H., Jr.: Rabbit Antipneumococcus Serum in the Therapy of Ulcus Serpens, J. A. M. A. **112**:2130 (May 27) 1939.

Haemophilus ducreyi, Pneumococcus, Corynebacterium diphtheriae, Neisseria gonorrhoeae, the diplobacillus of Morax and Haemophilus influenzae (Koch-Weeks bacillus) (Duke-Elder [3]). Moreover, as indicated hereafter, a bacteriologic diagnosis is of importance in the epidemiologic control of transmissible ocular diseases. It is desirable, therefore, to record the results of examinations conducted in the clinical and research laboratories of the Mount Zion Hospital during the past few years and to summarize the observations in the more common infections of the eye as reported in the literature.

II. TECHNICAL PROCEDURES

It is necessary to withhold treatment with germicides for at least twenty-four hours prior to examination. Since living bacteria are more apt to be located on conjunctival epithelium which has proliferated as a result of infection rather than in purulent secretions, it is best to remove the latter with saline solution or dry gauze. The eye is then anesthetized with 4 per cent cocaine or 0.5 per cent pontocaine hydrochloride, and material for cultures and smears is obtained by scraping the epithelium of the bulbar, palpebral, tarsal and retrotarsal conjunctivas with a platinum spatula (fig. 1). This instrument, which was introduced by Halberstaedter and von Prowazek [4] and popularized by Lindner,[5] Howard [6] and Finnoff,[7] is made by hammering 1.5 cm. of 16 Brown and Sharpe gage platinum wire into the form of a shovel, soldering it to 4 cm. of steel wire and mounting this on an alumi-

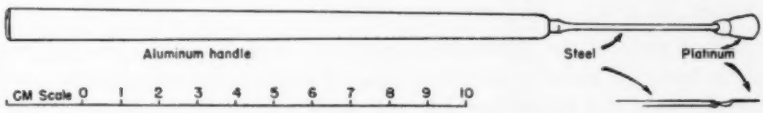

Fig. 1.—Spatula used in scraping the conjunctiva.

num handle. It is held at right angles to the surface of the conjunctiva, and a thin layer of epithelium is removed with one bold, gentle stroke, care being take to avoid bleeding. The bulbar conjunctiva is also examined, since, as was demonstrated by Lindner,[5] it may show evidence of bacterial growth several days earlier than the palpebral. Satisfactory results may also be obtained, according to Khorazo and Thompson,[8] by dipping a small sterile cotton swab into broth, rubbing the conjunctivas vigorously and inoculating culture mediums. It must be emphasized, however, that the swab is not suitable for the collection of cells which are to be stained for inclusion bodies, which are described hereafter. Under special circumstances, material may be removed from the margins of a corneal ulcer with the point of a Graefe knife, care being taken to avoid the pupillary area. The lacrimal duct is gently squeezed, and the pus which exudes is used for culture. In patients with angular conjunctivitis or with blepharoconjunctivitis, the margins of the lid are

3. Duke-Elder, W. S.: Text-Book of Ophthalmology, London, Henry Kimpton, Publisher, 1938, vol. 2, p. 1586.

4. Halberstaedter, L., and von Prowazek, S.: Ueber Zelleinschlüsse parasitärer Natur beim Trachom, Arb. a. d. k. Gsndhtsamte. **26**:43, 1907.

5. Lindner, K.: Ueber das Verhältnis der Erreger eitriger Bindehautentzündungen zur Hornhaut, Ztschr. f. Augenh. **53**:157, 1924; Ueber die Topographie der parasitären Bindehautkeime, Arch. f. Ophth. **105**:726, 1921.

6. Howard, H. J.: Role of the Epithelial Cell in Conjunctival and Corneal Infections, Am. J. Ophth. **7**:1909, 1924.

7. Finnoff, W. C.: Recognition of Epithelial Parasites, Am. J. Ophth. **7**:936, 1924.

8. Khorazo, D., and Thompson, R.: The Bacterial Flora of the Normal Conjunctiva, Am. J. Ophth. **18**:1114, 1935.

scraped. Occasionally it is advisable to examine follicles expressed by grattage or bits of conjunctiva removed at biopsy.

In addition to Petri plates containing rabbit blood agar, one should inoculate slants of Löfflers' medium and tubes of infusion broth. For the isolation of obligate or facultative anaerobes, tubes of Brewer's [9] thioglycollate broth and blood plates poured into Spray (anaerobic) dishes [10] are employed. Cornmeal, instead of Sabouraud agar, is used for the cultivation of fungi, while tubercle bacilli, gonococci, Pasteurella tularensis and Brucella melitensis require special mediums. A jar containing 30 per cent carbon dioxide is useful for the growth of gonococci, meningococci and certain strains of Br. melitensis.[11]

Material on the platinum spatula is also carefully spread over the surface of clean slides, and not rubbed, in order not to destroy the epithelial cells. In addition to the Beerman and Kopeloff modification of the Gram stain,[11] one employs Wright and Giemsa stains. The latter are particularly useful for the recognition of inclusion bodies.

Giemsa solution is prepared just before use as follows:

One drop of the commercial stain (Hynson, Westcott & Dunning, Inc., or National Aniline Division, Allied Chemical & Dye Corporation) is diluted with 4 cc. of distilled water, previously adjusted to p_H 7.8 by means of a phosphate buffer solution. The preparations, after being dried in the air, are fixed by being flooded with absolute ethyl or methyl alcohol (acetone free), which is allowed to evaporate. The slides are stained with the diluted dye for one hour or longer, the period depending on the results of preliminary trials. The staining is followed by drying in the air. When several slides are to be stained, it is preferable to employ a Coplin jar which is protected from sunlight.

It is well to remind the ophthalmologist that final bacteriologic reports are not made on the basis of stained smears alone. Fermentation and serologic tests and animal inoculations are necessary for the final identification of micro-organisms. Even in the case of the gonococcus or the Morax bacillus, a diagnosis by smear is of only presumptive nature.

The dark field condenser is of value when one is searching for evidence of infection due to spiral organisms, e. g., S. pallida in primary syphilitic infection of the lid, Treponema pertenue in frambetic conjunctivitis, Treponema vincenti in fusospirochetal infection, Leptospira icterohaemorrhagiae and Leptospira canicola in Weil's disease of the eye and Spirillum minus in the ocular lesions of ratbite fever (Bayne-Jones and Lerner [12]).

Inoculation of guinea pigs with bits of tissue or with secretions is indicated when oculoglandular tularemia, brucellosis or tuberculosis is suspected. Intratesticular or corneal injection into rabbits may be used in searching for S. pallida or for a virus. When one is testing for the latter, the eyelids and nictitating membrane of a rabbit are immobilized by means of a special speculum (fig. 2), and after careful anesthetization with cocaine and fixation of the eyeball, the cornea is scarified two or three times with the point of a scalpel, and the material is rubbed into its surface. By means of a fine needle, it is also possible to inject material subconjunctivally, into the anterior chamber or between the lamellas of the cornea. Intracerebral and intranasal injection into mice, rabbits, monkeys, Syrian hamsters or ferrets is practiced when one is searching for special types of viruses. Although

9. Brewer, J. H.: A Clear Liquid Medium for the Aerobic Cultivation of Anaerobes, J. Bact. **39**:10, 1940.

10. Spray, R. S.: Improved Anaerobic Culture Dish, J. Lab. & Clin. Med. **16**:203, 1930.

11. Manual of Methods for Pure Culture Study of Bacteria, Society of American Bacteriologists, Geneva, New York, Biotech Publications, 1941.

12. Bayne-Jones, S., and Lerner, M. L.: Ocular Lesions of Rat-Bite Fever in Guinea-Pigs, Arch. Ophth. **4**:858 (Dec.) 1930.

streptococci and pneumococci isolated from persons with conjunctival infections are usually not pathogenic for animals, it is nevertheless advisable to test for them and other bacteria by injecting material subcutaneously, intraperitoneally, intradermally and subconjunctivally.

Serologic reactions have assumed an important ancillary role in the diagnosis of ocular infections. In addition to the Wassermann test and flocculation tests, such as the Kahn, Eagle and Kline, for the diagnosis of syphilitic infections, including interstitial keratitis, syphilitic iritis and choroiditis (Browning,[13] Spanic [14]), the agglutination test, which is of aid in the recognition of oculoglandular tularemia (Vail,[15] Simpson,[16] Zwick,[17] Pfingst [18]) and Br. melitensis infections (Orlov,[19] Rutherford [20]), should be mentioned. In the former disease the titer may be 1:2,000 or more during the third week of illness. However, a positive reaction in a dilution of 1:160 is usually considered diagnostic (Kolmer and Boerner [21]). The reaction may be positive several years after recovery from the disease. Since recurrent iritis, iridocyclitis or neuroretinitis may be traceable to an infection with Br. melitensis (Green,[22] Nikolaeva [23]), the agglutination test with this antigen is of value. A diagnosis may be made if the titer of the serum reaches 1:100. The test may also be employed for the diagnosis of ocular manifestations of Weil's

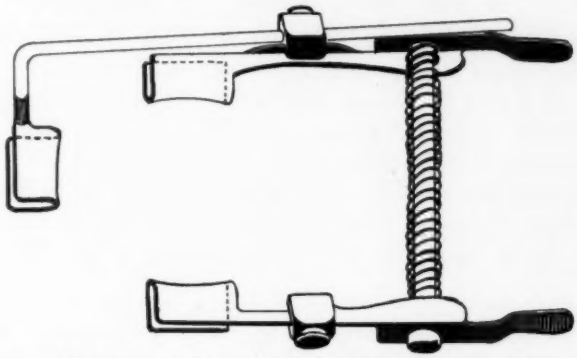

Fig. 2.—Speculum with retractor for holding the nictitating membrane of the rabbit's eye (after von Herrenschwand [51c]).

disease, due to L. icterohaemorrhagica or L. canicola (the canine type) (Legras and Wolters [24]). The agglutination test with various strains of Bacillus proteus,

13. Browning, S. H.: Syphilitic Diseases of the Eye, Brit. J. Ven. Dis. **6**:224, 1930.
14. Spanic, A.: Ein seltener Fall von nichtesulzerierter Bindehautsklerose der Uebergangsfalte des Unterlides, Ztschr. f. Augenh. **92**:300, 1937; cited by Hagedorn.[145l]
15. Vail, D. T., Jr.: (*a*) A Case of Bacillus Tularense (Squirrel Plague) Conjunctivitis, Arch. Ophth. **55**:235, 1926; (*b*) Oculoglandular Form of Tularemia, ibid. **2**:416 (Oct.) 1929.
16. Simpson, W. M.: Tularemia (Francis' Disease), Internat. S. Digest **6**:131, 1928; Tularemia (Francis' Disease), Ohio State M. J. **24**:860, 1928.
17. Zwick: Ueber Tularämie, Centralbl. f. allg. Path. **63**:92, 1935.
18. Pfingst, A. O.: Tularemia as it Involves the Eye, Kentucky M. J. **34**:307, 1936.
19. Orlov, K.: Melitococci (Maltafieber) und Auge, Zentralbl. f. d. ges. Ophth. **21**:438, 1929.
20. Rutherford, C. W.: Papilledema in Undulant Fever, J. A. M. A. **104**:1490 (April 27) 1935.
21. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technic, New York, D. Appleton-Century Company, Inc., 1931.
22. Green, J.: Ocular Manifestations in Brucellosis, Arch. Ophth. **21**:51 (Jan.) 1939.
23. Nikolaeva, M. S.: Clinical and Anatomico-Pathologic Changes of Eyes in Brucellosis, Vestnik oftal. **2**:187, 1937; cited by Pillat.[145g]
24. Legras, A. M., and Wolters, D. H. F.: Ophthalmologic Complications in a Case of Weil's Disease, Typus Canicola (Leptospira Canicola), Ophthalmologica **99**:469, 1940.

recently suggested as a diagnostic procedure for trachoma (Poleff [25]), has been found to be valueless by Thygeson [26] and Julianelle [27]). Likewise the presence of rickettsias in this disease (Foley and Parrot [28]) has been denied.

According to Edmund,[29] the complement fixation test is of value in the diagnosis of gonococcic iritis and iridocyclitis. A very strong positive reaction aids in differentiation of these infections from rheumatic iritis, whereas a weakly positive reaction indicates antibodies resulting from a past infection or from immunization with a vaccine. A negative reaction is of no significance (Bulloch [30]). The complement fixation reaction is also useful for the detection of the virus of lymphogranuloma venereum, which is one of the causes of the oculoglandular syndrome of Parinaud and may be a cause of other ocular diseases, particularly of inflammation of the uveal tract. Because of cross immunologic reactions, the virus of psittacosis may be substituted as an antigen (Macnie,[31] Appelmans [32]).

Brief reference may be made to the tuberculin, the brucellin and the Frei cutaneous test, which are useful as aids in the diagnosis of tuberculosis, brucellosis and lymphopathia venereum, respectively (Kolmer and Tuft [33]).

III. FACTORS GOVERNING THE RESISTANCE, IMMUNITY AND INFECTION OF THE CONJUNCTIVA AND CORNEA

The conjunctival epithelium varies, being stratified squamous at the margin of the lids, cylindric toward the convex border of the tarsal plate, columnar in the retrotarsal fold and fornix and again stratified squamous as it becomes adjacent to the sclera and cornea. Under normal conditions, when this mucous membrane is intact it is impermeable to bacteria. The same is true of the cornea, which is composed of a keratin-like substance, is largely avascular and obtains its nutrition by dialysis from the periphery. The tears which bathe these surfaces offer additional protection, being markedly bactericidal, owing in part to their content of lysozyme.[34]

25. Poleff, L.: Résultats de mes recherches au Maroc sur l'étiologie du trachome, Arch. roumaines de path. expér. et de microbiol. **10**:193, 1937; Seroreaktion von Weil-Felix bei Trachom, Klin. Monatsbl. f. Augenh. **101**:243, 1938.

26. Thygeson, P.: Problem of Rickettsias in Trachoma, Arch. Ophth. **20**:16 (July) 1938.

27. Julianelle, L. A.: The Etiology of Trachoma, New York, Commonwealth Fund, Division of Publications, 1938.

28. Julianelle, L. A., and Smith, J. E.: Studies on the Infectivity of Trachoma: IX. Immunological Aspects of the Rickettsial Concept, Am. J. Ophth. **23**:62, 1940. Foley, H., and Parrot, L.: Sur les formes d'évolution de rickettsia trachomatis, Arch. Inst. Pasteur d'Algérie **16**:283, 1938.

29. Edmund, C.: Die Gonokokkenkomplementbildungsreaktion und Iridocyclitis gonorrhöica, Acta ophth. **10**:151, 1938; abstracted, Zentralbl. f. d. ges. Ophth. **27**:638, 1932.

30. Bulloch, W., in A System of Bacteriology, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 2, p. 279.

31. Macnie, J. P.: Ocular Lymphogranuloma Venereum, Arch. Ophth. **25**:255 (Feb.) 1941.

32. Appelmans, M.: Conjonctivite infectieuse de Parinaud causée par le virus de la maladie de Nicolas-Favre, Ophthalmologica **96**:321, 1938.

33. Kolmer, J. A., and Tuft, L.: Clinical Immunology, Biotherapy and Chemotherapy, Philadelphia, W. B. Saunders Company, 1941.

34. For reviews and discussions of lysozyme, see: Ridley, F.: Lysozyme: An Antibacterial Body Present in Great Concentration in Tears, and Its Relation to Infection of the Human Eye, Proc. Roy. Soc. Med. **21**:1495, 1928. Roberts, E. A. H.; Maegraith, B. G., and Florey, H. W.: A Comparison of Lysozyme Preparations from Egg White, Cat and Human Saliva, Quart. J. Exper. Physiol. **27**:381, 1938; The Preparation of Purified Egg White Lysozyme, ibid. **27**:89, 1937. Thompson, R., and Gallardo, E.: The Antibacterial Action of Tears on Staphylococci, Am. J. Ophth. **24**:635, 1941. Thompson, R.: Lysozyme and Its Relation to the Antibacterial Properties of Various Tissues and Secretions, Arch. Path. **30**:1096 (Nov.) 1940.

This substance, which was discovered by Fleming,[35] is a polypeptide which in its reduced state exerts a lytic action on a variety of saprophytic and pathogenic bacteria. Among these are Micrococcus lysodeikticus, Sarcina, staphylococci, streptococci, gonococci, pneumococci, meningococci, the bacillus of dysentery, of anthrax and of paratyphoid fever, and Bacillus pyocyaneus. In its chemical properties lysozyme is different from bacteriophage. It acts through physical methods by lowering the surface tension (Meyer, Thompson, Palmer and Khorazo[36]). It is present in many animal and in some plant tissues, being high in concentration in the tears, cartilage and blood fibrin and low in the serum and leukocytes (Bradford and Roberts[37]). There is none in the aqueous humor, vitreous, cerebrospinal fluid or normal urine. As a result of a diet insufficient in vitamin A or of excessive tearing, as in the presence of a foreign body, in conjunctivitis or in trachoma, there is a marked fall in the lysozyme content of the tears (Hallauer[38]).

The various phases of an inflammatory process in the eye must be regarded as part of the defense mechanism (Menkin[39]). The epithelial cells of the conjunctiva and the polymorphonuclear leukocytes which arrive in response to an infection function as phagocytes (Howard[6]). The conjunctival epithelium proliferates during infection, thus permitting the uppermost layers, which contain bacteria, to be cast off. There is increased permeability of the capillaries during inflammation and after paracentesis of the cornea, which allows antibodies from the blood stream to pass into the conjunctival secretions and the aqueous and vitreous humors. Except when a conjunctival infection is part of a generalized invasion, as in undulant fever or tularemia, the content of bactericidal antibodies and opsonins in the conjunctival secretions and ocular fluids is low (zur Nedden[40]).

There is a species resistance in ocular infections. Thus, human beings are susceptible to their own varieties of infective organisms, such as the gonococcus, H. influenzae and the virus of trachoma, to which the lower animals, except monkeys and anthropoid apes, are generally immune. The relative immunity of the conjunctiva and cornea is not shared by the interior parts of the eye, where there are normally low concentrations of immune substances. Thus, so-called harmless bacteria, e. g. Bacillus subtilis, B. pyocyaneus (Pseudomonas aeruginosa) and a number of "saprophytic" molds, may produce panophthalmitis when they have penetrated into the anterior chamber or the vitreous.

In many infectious diseases of the eye, e. g. "pink eye" and trachoma, there seems to be no permanent immunity as a result of one or more attacks. The existence of a carrier state has been established for infections due to H. influenzae, the Morax bacillus, Pneumococcus and Gonococcus (zur Nedden[41]).

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35. Fleming, A.: On a Remarkable Bacteriolytic Element Found in Tissues and Secretions, Proc. Roy. Soc., London, s.B **93**:306, 1922.

36. Meyer, K.; Thompson, R.; Palmer, J. W., and Khorazo, D.: The Purification and Properties of Lysozyme, J. Biol. Chem. **113**:303, 1936; On the Mechanism of Lysozyme Action, ibid. **113**:479, 1936.

37. Bradford, W. L., and Roberts, J. B.: The Lysozyme Content of Blood, J. Pediat. **8**:24, 1936.

38. Hallauer, C.: Klinische und experimentelle Untersuchungen über den Lysozymgehalt im Bindehautsack und in der Tränenflüssigkeit, Arch. f. Augenh. **103**:199, 1930.

39. Menkin, V.: Dynamics of Inflammation, New York, The Macmillan Company, 1940.

40. zur Nedden, M.: Ueber das Vorkommen bakterizider Substanzen in Bindehautsekret, Ber. ü. d. Versamml. d. ophth. Gesellsch. **33**:36, 1907; Ueber die Bedeutung der Opsonine für das Auge, Ztschr. f. Augenh. **19**:314, 1908.

41. zur Nedden, M.: Die Bakterienflora des Auges, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1937, vol. 2, p. 984.

Infections of the conjunctiva and cornea are usually preceded by an injury with a foreign body. However, trauma to a baby during passage through the birth canal may suffice. Vitamin depletion, particularly of vitamin A, may lead to increased susceptibility to infection. Infections may be embolic or hematogenous in origin or due to an extension from one eye to another or from the scalp or the adjacent skin. Focal infections in the teeth, tonsils, sinuses (Cullom [42]), gallbladder, prostate or other part of the urinary tract may lead to invasion of the ocular tissues by bacteria or their toxins. In experimental animals it is possible to produce a lowered resistance of the conjunctiva by blocking the cells of the reticuloendothelial system. Closure of the tear duct or canaliculus, with interference in the flow of tears, usually results in a lacrimal conjunctivitis.

During the course of conjunctivitis, bacteria may lodge and multiply on the cornea without producing evidence of keratitis. A number of virulent and toxin-producing micro-organisms may, however, invade the cornea and produce severe damage. Among these are the gonococcus, the pneumococcus and several viruses, which will be listed. Although the corneal epithelium is unable to phagocytose

TABLE 1.—*Etiologic Classification of 261 Cases of Ophthalmia Neonatorum (from Thygeson [43])*

	Number	Percentage
Etiologic agent determined:		
Staph. aureus (hemolytic)	135	51.7
D. pneumoniae (pneumococcus)	34	13.0
Inclusion blennorrhea virus	23	8.8
D. pneumoniae and Staph. aureus	15	5.7
H. influenzae	7	2.6
Lacrimal conjunctivitis (D. pneumoniae, 2; Staph. aureus, 3)	5	1.9
Esch. coli	2	0.76
Str. viridans	2	0.76
Staph. aureus and H. influenzae	3	1.1
Neisseria gonorrhoeae	1	0.38
Unknown cause: Flora normal (C. xerosis, C. hofmanni, Staph. albus) or absent	34	13.0
	261	
Incidence of ophthalmia neonatorum in 3,939 newborn infants		6.6
Incidence of gonorrheal ophthalmia		0.022

bacteria, its upper layers are capable of proliferation and shedding, thus disposing of some of the bacteria.

IV. CONJUNCTIVITIS OF THE NEWBORN

A bacteriologic diagnosis in conjunctivitis of the newborn is important for the epidemiologic control of the nursery, the hospital wards and the personnel, as well as for determining the therapy and prognosis in the case. My associates and I, as well as Thygeson [43] and MacCallan,[44] have observed that gonorrheal ophthalmia of the newborn (Sweet [45]) is now seldom found in modern communities. The micro-organisms most frequently encountered are staphylococci, Escherichia coli, pneumococci, diphtheroids and Micrococcus catarrhalis (table 1). Influenza bacilli and B. subtilis have also been reported (Browning [46]). When no bacteria can

42. Cullom, M. M.: Effect of Sinus Diseases on the Eye, South. M. J. **32**:743, 1939.

43. Thygeson, P.: Ophthalmia Neonatorum: A Study of Two Hundred and Sixty-One Cases, Tr. Am. Ophth. Soc. **34**:340, 1936.

44. MacCallan, A. F.: Rôle of the Gonococcus in Purulent Ophthalmia in Warm Climates, Arch. Ophth. **12**:819 (Dec.) 1934.

45. Sweet, L. K.: Gonococcic Conjunctivitis in Children, J. Pediat. **19**:1, 1941.

46. Browning, S. H.: Bacteriology of Ophthalmia Neonatorum, Tr. Ophth. Soc. U. Kingdom **56**:24, 1936.

be cultivated and inclusion bodies are absent, it is well to bear in mind that the Credé treatment may produce a chemical conjunctivitis. In a 3 day old infant Batignani [47] observed conjunctivitis and keratitis due to the herpes virus. The mother had had premenstrual herpes.

For the past nine years, in reports covering approximately 3,700 births my associates and I at the Mount Zion Hospital discovered 1 case of inclusion blennorrhea. A second was referred to us from another institution in San Francisco. The first baby was seen by Dr. Frank Rodin five days after birth, Oct. 21, 1932, with a purulent discharge from both eyes. The father had had gonorrhea, and the mother had suffered from a vaginal abscess. No bacteria could be cultivated under either aerobic or anaerobic conditions, but scrapings from the tarsal and the

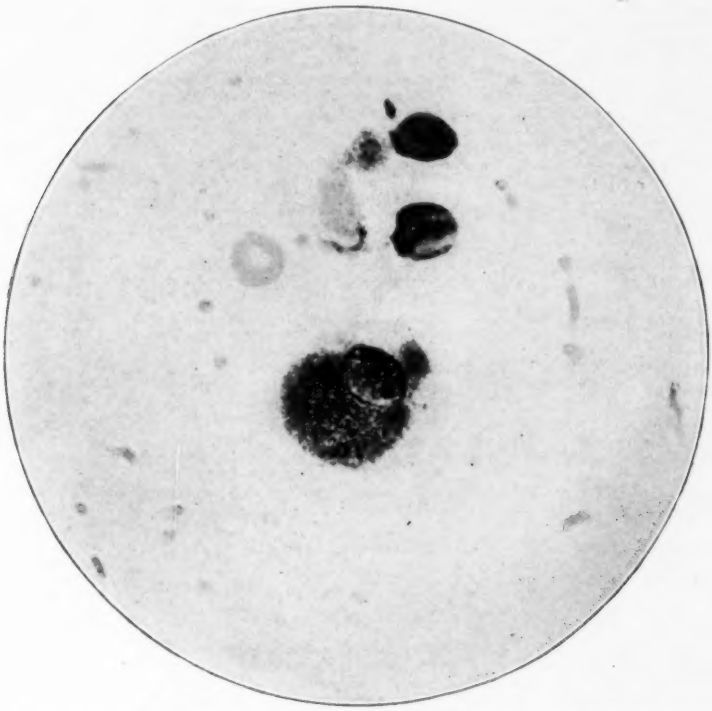

Fig. 3.—Epithelial cell showing cytoplastic inclusions (my preparation) from a newborn baby with inclusion blennorrhea observed at the Mount Zion Hospital.

palpebral conjunctivas showed epithelial, cytoplasmic inclusions characteristic of inclusion blennorrhea. The discharge continued for several months, but there were no corneal complications (fig. 3). The second child was seen by Dr. George Lachman on Oct. 10, 1942, approximately thirteen days after birth. The lids of both eyes were edematous and showed a mucopurulent discharge. In scrapings stained with Giemsa solution we demonstrated the characteristic inclusion bodies. Local instillations of 5 per cent sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) solution brought about recovery in a few days.

47. Batignani, A.: Congiuntivite da virus erpetico in neonato, Boll. d'ocul. **13**:1217, 1934; cited by Pillat.[145e]

A brief summary of the etiology of inclusion conjunctivitis is here presented.[48] The disease is a distinct clinical entity, characterized by a period of onset of from five to ten days after birth, a duration of from three to four months and the presence of cytoplasmic inclusion bodies in the conjunctival epithelial cells. It is transferable to the adult human conjunctiva, where it produces a papillary or follicular conjunctivitis. It is due to a filtrable virus, since the causative agent will not grow on artificial mediums and will pass through Elford membranes which retain ordinary

TABLE 2.—*Results of Bacteriologic Examinations in Conjunctivitis of the Newborn*

Patient, Date, Sex, Age	Clinical Data	Bacteriologic Observations	Special Treatment and Results
Baby T., 10/21/32, ♀, 5 days	Five days after birth, child showed purulent discharge from both eyes; father had gonorrheal urethritis; mother had vaginal abscess during pregnancy	Vaginal smear of mother negative; scrapings from baby's tarsal and palpebral conjunctivas showed epithelial cell inclusions characteristic of inclusion blennorrhea; no bacteria in smear or culture	Irrigation with saline solution 3 times daily; purulent discharge continued for several months
J. M. G., 10/14/41, ♀, 21 days	Thirteen days after birth, swelling and discharge, left eye; right eye involved; 8 days later, lids edematous and red; purulent secretion	Cytoplasmic bodies characteristic of inclusion blennorrhea; nontoxigenic Staph. albus	Instillation of 5 per cent sulfathiazole solution; prompt recovery
Baby P., 5/6/38, ♂, 3 days	Three days after birth, purulent secretion from right eye	Smear, few epithelial cells, no bacteria or inclusion bodies; culture, several colonies of Staph. albus, occasional colonies of nonhemolytic streptococci and Str. viridans, also a few diphtheroids	.....
Baby M., 5/20/38, 2-3 days	Purulent discharge from right eye	Gram stain, many pus cells, no bacteria, no inclusion bodies; culture, Staph. albus and a few diphtheroids	.....
Baby T. R., 7/16/39, 11 days	Purulent discharge from left eye	Smear, gram-positive cocci and leukocytes, also few gram-negative rods; culture, Staph. aureus (hemolytic)	.....
Baby N., 9/18/33, 2 days	Purulent discharge from both eyes	Smear, epithelial cells, diphtheroid bacilli, no inclusion bodies; culture, Staph. albus and diphtheroids	.....
Baby G., 10/17/33, ♀, 2 days	After birth, greenish discharge from both eyes	Culture, Staph. albus (hemolytic), Staph. aureus and diphtheroids	.....
Baby K., 1/26/39, 2 days	Conjunctivitis, left eye, at birth; eczema of face	Direct smear, no bacteria; culture, Staph. aureus	.....
C. T., 1/22/40, ♀, 7 mo.	Infection began 3 days after birth, with purulent discharge	Pneumococcus type III	After failure of treatment with silver nitrate, zinc sulfate and sulfanilamide, the infection was cleared up promptly with optochin hydrochloride
Baby C., 5/2/37, 1 day	Two hours after birth, swelling and discoloration of upper lids, especially in left eye; purulent secretion	Direct smear, numerous white blood cells; culture, no growth	Irrigation with saline solution; chemical irritation (silver nitrate) cleared up in a few days

48. For literature on inclusion conjunctivitis, see: (*a*) James, W. M.: Inclusion Blennorrhea, Am. J. Ophth. **13**:1084, 1930. (*b*) Julianelle, L. A.: Relation of Inclusion Blennorrhea to Swimming-Bath Conjunctivitis as Determined by an Accidental Transmission, Proc. Soc. Exper. Biol. & Med. **36**:617, 1937. (*c*) Julianelle, L. A.; Harrison, R. W., and Lange, A. C.: Studies on Inclusion Blennorrhea Through Accidental Transmission, Am. J. Ophth. **21**:1137, 1938; (*d*) Studies on the Infectious Agent of Inclusion Blennorrhea, Am. J. Path. **14**:579, 1938. (*e*) Julianelle, L. A., and Lange, A. C.: Studies on Inclusion Blennorrhea: I. Clinical and General Observations, Am. J. Ophth. **21**:890, 1938. (*f*) Julianelle, L. A.; Harrison, R. W., and Lange, A. C.: Studies on Inclusion Blennorrhea: II. Experimental Transmission, ibid. **21**:1137, 1938; (*g*) III. Experimental Considerations of the Etiology, ibid. **21**:1230, 1938. (*h*) Morax, V.: Les conjonctivites folliculaires, Paris, Masson & Cie, 1933. (*i*) Thygeson, P.: The Etiology of Inclusion Blennorrhea, Am. J. Ophth. **17**:1019, 1934. (*j*) Thygeson, P., and Mengert, W. F.: The Virus of Inclusion Conjunctivitis, Arch. Ophth. **15**:377 (March) 1936. (*k*) Thygeson, P.: Treatment of Inclusion Conjunctivitis with Sulfanilamide, ibid. **25**:217 (Feb.) 1941; (*l*) The Treatment of Inclusion Conjunctivitis with Sulfanilamide, Tr. Am. Ophth. Soc. **76**:111, 1940. (*m*) Thygeson, P., and Stone, W., Jr.: Epidemiology of Inclusion Conjunctivitis, Arch. Ophth. **27**:91 (Jan.) 1942.

bacteria. The virus has been demonstrated in the cervical epithelium of the mothers of infected infants and in the urethra of the fathers. Julianelle, Harrison and Lange have transferred the disease to rhesus monkeys and baboons, in which it is clinically indistinguishable from swimming bath conjunctivitis or trachoma.[49]

The inclusion bodies (fig. 4) are of two types—initial bodies, which stain strongly blue with Giemsa stain, and elementary bodies which show both the pink

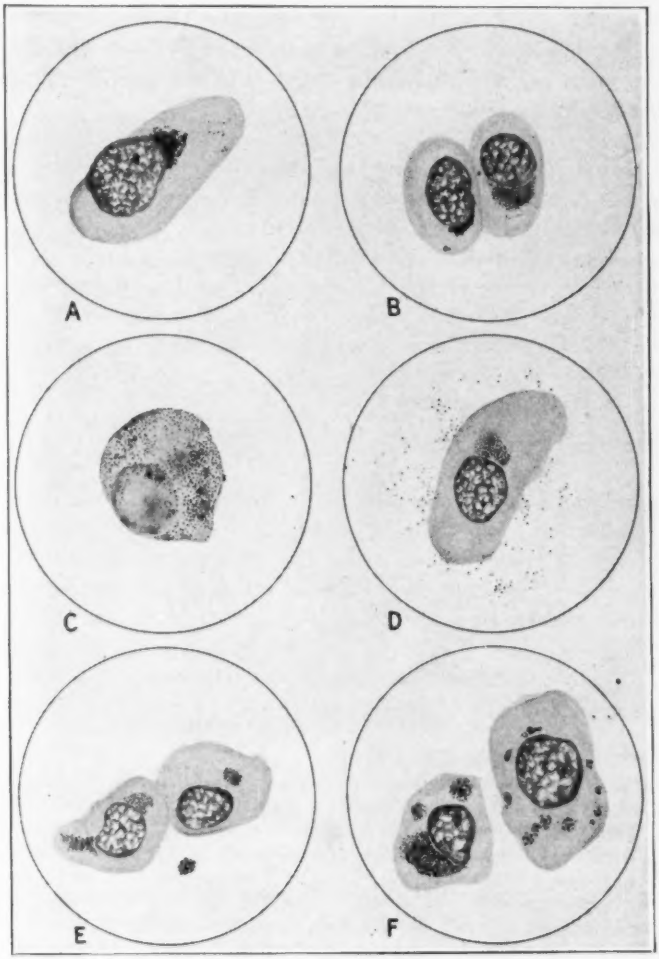

Fig. 4.—Several preparations showing inclusion bodies: *A*, *B* and *C*, modified from Thygeson,[18i] which illustrate elementary and initial body stages, are from a case of inclusion blennorrhea. *A* shows an intermediate inclusion. In *B*, the body on the right is an elementary body inclusion and that on the left an initial body inclusion. *C* shows a large elementary body inclusion. A few initial bodies remain; the nucleus is undergoing degeneration. *D*, *E* and *F*, modified from Julianelle,[27] illustrate inclusion bodies; *D*, an inclusion body of trachoma, composed entirely of elementary bodies, some located extracellularly; *E*, inclusions of trachoma, composed of initial bodies, one extracellular clump suggesting the morula stage of certain viruses, and *F*, inclusions observed in inclusion blennorrhea (note the mixed elementary and initial bodies in the cell to the left and the multiple inclusions of the initial bodies in the cell to the right).

49. Julianelle and Lange.[48e] Julianelle, Harrison and Lange.[48f]

and the blue staining reaction. The elementary bodies are constantly present in the conjunctiva and multiply in the new host when the disease is transferred from patient to patient. Filtrates which do not contain elementary bodies are not infective. The elementary bodies are minute granules of uniform size, about 0.25 micron in diameter; they stain a reddish blue with Giemsa stain and poorly and slowly with ordinary aniline dyes. They are gram-negative and resemble closely the elementary bodies characteristic of vaccinia, fowlpox and psittacosis. They are uniform in size, are frequently diplococcic in form and stain a reddish blue with Giemsa stain. The initial bodies are coccobacillary in shape and vary from 0.3 to 0.8 micron in diameter. They stain blue dipolarly with Giemsa solution, are gram-negative, stain poorly with aniline dyes and are similar to the large forms of the psittacosis virus (Thygeson [48l]).

According to Thygeson the inclusion bodies are intracellular colonies of elementary and initial bodies in various stages of development.[50] The smallest inclusions are made up entirely of initial bodies, and the largest ones, which in the early stages of the disease may entirely replace the cytoplasm of the cell, are made up entirely of elementary bodies. The free elementary body (which is the infectious agent) penetrates an epithelial cell and develops into an initial body. The initial body then divides and becomes progressively smaller until the elementary body stage is reached. The cell may now rupture, and the elementary bodies are scattered into the secretions.

V. BACTERIA IN THE MORE COMMON INFECTIONS OF THE CONJUNCTIVA AND EYELIDS[51]

The bacterial flora of infections of the conjunctiva vary with the geographic location and occupation of the patient. They also seem to change from generation to generation, as sanitation, nutrition and bacteriologic technic improve. Thus, in Glasgow, Michaelson [52] recently reported on the rarity in adults of conjunctivitis due to the Koch-Weeks bacillus while in Cagliari, Italy, this organism is still common. In Egypt, Meyerhof [53] reported in 1932 on the extensive presence of Gonococcus, H. influenzae, Bacillus duplex and pneumococci in endemic conjunctivitis. In San Francisco the hemolytic and toxigenic variety (fig. 5) of Staphylo-

50. Thygeson.[48l] Thygeson and Mengert.[48j]

51. For general discussions of the more common infections of the conjunctiva and eyelids, see: (*a*) Axenfeld, T.: Bacteriology of the Eye, translated by A. Macnab, London, Baillière, Tindall & Cox, 1908. (*b*) Infektionen der Conjunctiva, in Kolle, W.; Krauss, R., and Uhlenhuth, P.: Handbuch der pathogenenen Microorganismen, ed. 3, Jena, Gustav Fischer, 1928, vol. 6, p. 281. (*c*) von Herrenschwand, F.: Die Pathogenen Mikroorganismen des Auges, Berlin, Urban & Schwarzenberg, 1927. (*d*) Bayer, G., and von Herrenschwand, F.: Ueber die durch Bakterien aus der Gruppe des Bacillus pseudotuberculosis rodentium hervorgerufene Bindehautentzündung (Parinaudsche Conjunctivitis), Arch. f. Ophth. **98**:342, 1919. (*e*) Schieck, F.: Die Erkrankungen der Conjunctiva, Cornea und Sclera, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 4, pp. 124-133. (*f*) Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, P. Blakiston's Son & Co., 1942, vol. 2. (*g*) Thygeson, P.: Etiologic Diagnosis of Conjunctivitis, Arch. Ophth. **12**:676 (Nov.) 1934; (*h*) Treatment of Conjunctivitis, ibid. **19**: 586 (April) 1938; (*i*) The Cultivation of Conjunctivitis and Keratitis-Producing Agents on the Chorioallantoic Membrane of Chick Embryo, Am. J. Ophth. **23**:1217, 1940. (*j*) Wood, M. A.: A Study of Methemoglobin Producing Organism in Ocular Inflammations, ibid. **22**: 1111, 1935. Howard.[6] zur Nedden.[41]

52. Michaelson, I. C.: Conjunctivitis: A Clinical and Bacteriological Investigation, Glasgow M. J. **123**:185, 1935.

53. Meyerhof, M.: Ueber Conjunctivitis catarrhalis acuta in Aegypten, Klin. Monatsbl. f. Augenh. **94**:680, 1935; cited by Pillat.[145e]

coccus aureus [54] has been found to be the most common cause of a certain clinical type of conjunctivitis. Thygeson [55] described this disease as characterized by a prolonged duration and resistance to local treatment and as complicated by blepharitis and marginal ulcer of the cornea. Treatment with staphylococcus toxoid combined with autogenous vaccine has given good results in a number of cases (Burky,[54a] Julianelle, Boots and Harrison [56]). Local instillation of a solution of sulfathiazole is recommended in the acute stages of the infection.

As shown in table 3, other organisms also occur. Thus, from a patient with long-standing chronic dacryocystitis who had just recovered from influenza, we isolated Streptococcus haemolyticus. This organism, as noted by Kluever,[57] rarely produces catarrhal conjunctivitis but is a common cause of chronic, nondiphtheritic,

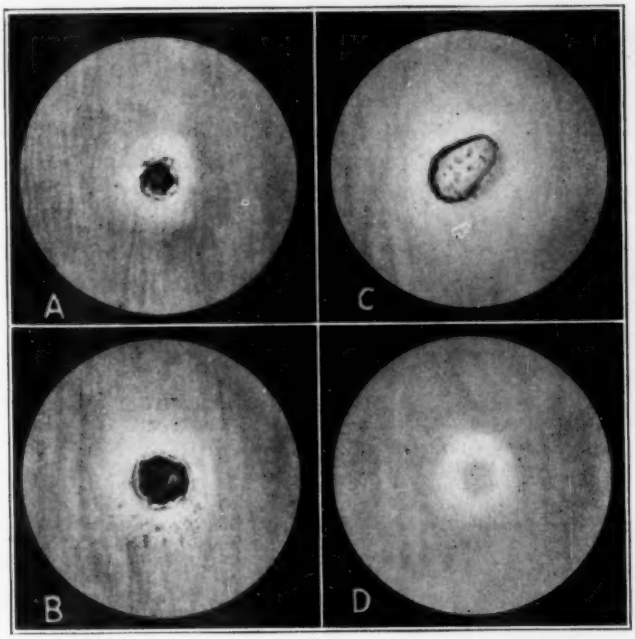

Fig. 5.—*A*, *B* and *C*, necrosis in the skin of a Javanese monkey (Macacus irus) given three intradermal injections of 0.05, 0.10 and 0.20 cc., respectively, of staphylococcus toxin in the presence of one-fifth unit of antitoxin. *D* shows the control spot, where 0.20 cc. of heated toxin was injected.

54. For literature on the toxigenicity of staphylococci, see: (*a*) Burky, E. L.: Staphylococcus Toxin and Antitoxin: Experimental and Clinical Studies with Special Reference to Ophthalmology, Internat. Clin. **3**:257, 1936; (*b*) Studies on the Action of Staphylococcus Toxin and Antitoxin with Special Reference to Ophthalmology, Am. J. Ophth. **19**:841, 1936. (*c*) Fairbrother, R. W.: Coagulase Production as a Criterion for the Classification of the Staphylococci, J. Path. & Bact. **50**:83, 1940. (*d*) Thygeson, P.: Mannitol Fermentation as an Indicator of Conjunctival Pathogenicity of Staphylococci, Arch. Ophth. **20**:274 (Aug.) 1938. (*e*) Thompson, R., and Khorazo, D.: Correlated Antigenic and Biochemical Properties of Staphylococci, J. Bact. **34**:69, 1937. (*f*) Weiss, C.: A Study of Natural and Acquired Immunity to Staphylococcal Toxin in Monkeys, J. Immunol. **37**:185, 1939.

55. Thygeson, P.: Bacterial Factors in Chronic Catarrhal Conjunctivitis: I. Role of Toxin-Forming Staphylococci, Arch. Ophth. **18**:373 (Sept.) 1937; Treatment of Staphylococcic Conjunctivitis with Staphylococcus Toxoid, ibid. **20**:271 (Aug.) 1938.

56. Julianelle, L. A.; Boots, R. H., and Harrison, G. H.: The Treatment of Staphylococcal Infections of the Eye by Immunization with Toxoid, Am. J. Ophth. **25**:431, 1942.

57. Kluever, H. C.: Streptococcic Inflammation of the Eye, Am. J. Ophth. **18**:805, 1935; Streptococcal Pseudomembranous Conjunctivitis, ibid. **18**:1094, 1935.

pseudomembranous conjunctivitis and of lacrimal conjunctivitis. We also cultivated Pneumococcus (Diplococcus pneumoniae) type XI in material from a lid abscess of a man who was suffering from pansinusitis and Streptococcus viridans in material from a similar lesion in a child with lipoid nephrosis. From a fourth patient, a California miner, who acquired acute conjunctivitis after an injury with slag dust, we isolated Bacillus faecalis alcaligenes (Alcaligenes faecalis), Staph. aureus and diphtheroids. Yakovleva [58] cited other instances of conjunctival infection due to A. faecalis. An epidemic of conjunctivitis due to this organism is referred to hereafter (Barrow [59]).

A number of other micro-organisms have been reported as causing infections of the conjunctiva. The pneumococcus is the commonest cause of so-called catarrhal

TABLE 3.—*Results of Bacteriologic Examinations in Infections of the Conjunctiva and Eyelids*

Patient, Sex, Date, Age	Clinical Data	Bacteriologic Observations
R. S., ♂, 1/13/34, child	Abscess, right lower lid; erythema nodosum and otitis media; styes	Blood culture negative; leukocytes 18,000 to 22,000; culture, Staph. aureus (hemolytic), right eye
C. S., ♂, 7/16/36, 59	Acute catarrhal conjunctivitis, right eye	Staph. albus and diphtheroids, no inclusion bodies; white blood cells, 25,400
R. S., ♂, 10/16/36, 31	Left eye, marginal chalazion in 1935, phlyctenule at limbus in 1935, recurrence in 1936; acute catarrhal conjunctivitis, mild degree, both eyes, 1936	Direct smear, no organisms or inclusion bodies; culture, Staph. aureus and albus, diphtheroids; B. proteus
M., ♂, 10/2/39 12/16/39, 48	12/16/39, chronic catarrhal conjunctivitis, abscessed teeth, infection of bulbar and palpebral conjunctivas and antrum; readmitted 2/23/40, furunculosis and conjunctivitis of left eye, also furuncles of right elbow, right knee and left ear	Culture, Staph. aureus (hemolytic) from eye, tooth and furuncle of hand
A. V., ♀ 12/6/40, 39	Infected eye while in transit across Siberia; styes on left eye; conjunctivitis	Culture, Staph. aureus (hemolytic) and diphtheroids
M. K., ♀, 1/15/41, 53	Chronic conjunctivitis and styes	Culture, Staph. albus and aureus (toxigenic)
H. B., 1/24/41	Hordeolum, both eyes; chronic otitis media	Culture, Staph. aureus (hemolytic), toxigenic
S. L., ♀, 12/10/41, 52	One week after influenzal attack inflammation of face, lids and lacrimal duct developed; conjunctivitis, left eye; treated in past for chronic dacryocystitis	Culture, Str. haemolyticus and Staph. aureus (nontoxigenic)
C. P., ♂, 11/12/35, 2	Lipoid nephrosis; abscess of lower left lid; bronchitis and rhinitis; purulent foul discharge from eyelid	Culture, Str. viridans; blood culture negative; antrum, Str. viridans
F. S., ♂, 4/3/39, 25	Periorbital swelling; pansinusitis; abscess of right lid	Direct smear, gram-positive diplococci, lancet shaped; culture, Pneumococcus type XI
J. B. G., ♂, 2/13/42, 36	Chronic conjunctivitis following slag dust in eye; mucopurulent discharge; no response to treatment	Culture, A. faecalis, toxigenic Staph. aureus and diphtheroids

conjunctivitis. "Pink eye" is usually caused by the Koch-Weeks bacillus, which is now recognized by Bergey's manual [60] as identical with H. influenzae (Schneider,[61] Durand and Lumbroso [62]), while angular conjunctivitis is produced by the diplo-

58. Yakovleva, A. A.: Familial Epidemic of Acute Catarrhal and Croupous Conjunctivitis Caused by Intestinal Bacteria, Sovet. vestnik oftal. **9**:354, 1936; cited by Hagedorn.[1451]

59. Barrow, R. H. B.: An Epidemic of Conjunctivitis Due to Infection with Bacillus Faecalis Alkaligenes, Brit. J. Ophth. **15**:319, 1931.

60. Bergey, D. H.; Breed, R. S.; Murray, E. G. D., and Hitchens, A.: Bergey's Manual of Determinative Bacteriology, ed. 5, Baltimore, Williams & Wilkins Company, 1939.

61. Schneider, R.: Vergleichende Untersuchungen über den Koch-Weeksschen Bazillus und das Pfeiffersche Influenzastäbchen, Arch. f. Hyg. **93**:26, 1923.

62. Durand, P., and Lumbroso, U.: Quelques caractères du bacille de Weeks. Ses rapports avec le bacille de Pfeiffer, Compt. rend. Soc. de biol. **94**:1322, 1926.

bacillus of Morax (H. duplex) (Reis [63]). The following micro-organisms are also pathogenic for the human conjunctiva: C. diphtheriae (Francois,[64] McKee [65]), Neisseria intracellularis (Meningococcus) (Gifford and Day [66]), Neisseria catarrhalis (Hamburger [67]), Past. tularensis, Esch. coli, Proteus vulgaris, M. (Bacillus) mallei (Ivanov [68]), Klebsiella pneumoniae (Friedländer's bacillus), Mycobacterium tuberculosis (Samuelson,[69] McKenzie [70]) and Mycobacterium leprae (Fuchs [71]). Cardell [72] stated that conjunctivitis due to B. pyocyaneus has a grave prognosis. McKee [73] reported the incidence of various types of pneumococci in 63 cases of conjunctivitis as follows: the types of group IV in 54 cases, type I in 5, type II in 1 and type III in 3. Anaerobic bacilli, including fusobacteria (von Herrenschwand,[74] Dunnington and Khorazo [75]), and spirochetes are occasionally incriminated.

Gonorrheal ophthalmia has become relatively rare and is now seldom seen in adults (Newsholme [76]). The syndrome known as Parinaud's conjunctivitis has been shown to be due to a variety of agents, among them Past. tularensis (Kogan,[77] Mickevic [78]), Myco. tuberculosis (von Szily [79]), leptothrix (Verhoeff [80]) and the virus of lymphogranuloma venereum (Macnie,[31] Appelmans [32]). Other virus infections of the eye are listed hereafter in section XIII.

Primary chancres, ulcers and gummas of the eyelids (due to S. pallida) have been reported by Appelbaum,[81] Lipovskaya,[82] McKee [83] and others. Infection of

63. Reis, W.: Klinische und experimentelle Untersuchungen über den Morax-Axenfeld Diplobazillus, Klin. Monatsbl. f. Augenh. **48**:529, 1910.

64. Francois, J.: Catarrhal Diphtheritic Conjunctivitis, Brit. J. Ophth. **19**:1, 1935.

65. McKee, S. H.: Two Cases of Diphtheria of the Conjunctiva, Canad. M. A. J. **35**:425, 1936; Diphtheria of the Conjunctiva, Tr. Am. Ophth. Soc. **34**:102, 1936.

66. Gifford, S. R., and Day, A. A.: Acute Purulent Conjunctivitis Due to the Meningococcus, Arch. Ophth. **13**:1038 (June) 1935.

67. Hamburger, F. A.: Akute Conjunctivitis, hervorgerufen durch den Micrococcus catarrhalis, Arch. f. Ophth. **135**:277, 1936.

68. Ivanov, A.: Case of Glanders of Eyelids, Sovet. vestnik oftal. **7**:403, 1936; cited by Pillat.[145f]

69. Samuelson, A.: Primary Tuberculosis of the Conjunctiva, Arch. Ophth. **15**:975 (June) 1936.

70. McKenzie, W. H.: Tuberculosis of the Conjunctiva, Am. J. Ophth. **22**:744, 1939.

71. Fuchs, A.: Ueber Leprabazillen in klinisch normal erscheinenden Augen, Klin. Monatsbl. f. Augenh. **98**:728, 1937; cited by Pillat.[145g]

72. Cardell, J. D. M.: Ophthalmia Neonatorum: General Considerations, Tr. Ophth. Soc. U. Kingdom **56**:3, 1936; cited by Hagedorn.[145i]

73. McKee, S. H.: Study of Pneumococcus Group from Inflamed Conjunctiva and Lacrimal Sac, Am. J. Ophth. **18**:1021, 1935.

74. von Herrenschwand, F.: Spirochaeten und Bacillus fusiformis bei akuter Konjunctivitis, Ztschr. f. Augenh. **62**:370, 1927.

75. Dunnington, J. H., and Khorazo, D.: Conjunctivitis Due to Fusospirochetal Infection, Arch. Ophth. **16**:252 (Aug.) 1936.

76. Newsholme, H. P.: Ophthalmia Neonatorum: Administrative Aspects, Tr. Ophth. Soc. U. Kingdom **56**:15, 1936; cited by Hagedorn.[145i]

77. Kogan, N., cited by Pillat.[145f]

78. Mickevic, L.: Okulo-glandularer Typus der Tularämie als einer der ätiologischen Faktoren des Parinaudschen Syndrome, Zentralbl. f. d. ges. Ophth. **27**:132, 1932.

79. von Szily, A.: Uebertragungsversuche mit Trachommaterial auf Hühner. Weiterer Beitrag zur Kenntnis der sog, Klin. Monatsbl. f. Augenh. **94**:753, 1935; cited by Pillat.[145f]

80. Verhoeff, F. H.: Leptothrix Conjunctivae Without Glandular Involvement, Arch. Ophth. **20**:1 (Jan.) 1941.

81. Appelbaum, A., cited by Hagedorn.[145h]

82. Lipovskaya, A.: Gumma of the Lids and Conjunctiva, Vestnik oftal. **15**:88, 1939: abstracted, Arch. Ophth. **25**:517 (March) 1941.

83. McKee, S. H.: Syphilitic Ulcer of Eyelid, Canad. M. A. J. **35**:307, 1936.

an infant's lids may occur during prolonged labor or as a late manifestation of congenital syphilis. Nonvenereal infection may arise as the result of a custom prevalent in Eastern Europe of kissing children's eyelids or of licking them in an effort to remove the "evil spirit" during an illness. There are also frambesic conjunctivitis, due to T. pertenue, and ocular manifestations of Weil's disease, due to L. icterohaemorrhagica and L. canicola.[24] Rarely one sees a conjunctival infection due to the bacillus of soft chancre (H. ducreyi) and one due to Pasteurella pseudotuberculosis rodentium [84] (table 4).

TABLE 4.—*Results of Laboratory Studies in the Principal Types of Conjunctivitis* *

Type of Conjunctivitis	Results of Laboratory Studies (Culture, Smear, Cutaneous Test, etc.)
1. Hyperacute	N. gonorrhoeae, rarely N. intracellularis
2. Acute and subacute	D. pneumoniae; Staph. aureus; H. influenzae; Str. haemolyticus; Esch. coli, etc.
3. Chronic catarrhal	Staph. aureus, H. duplex, etc.
4. Lacrimal	D. pneumoniae, H. influenzae, etc.
5. Pseudomembranous	C. diphtheriae or Str. haemolyticus
6. Accompanying oculoglandular tularemia	Agglutination with patient's serum positive after first week; guinea pig inoculation with material from lesions positive for Past. tularensis
7. Tuberculous	Guinea pig inoculation positive; culture on Corper's, Löwenstein's and other special mediums positive; reaction to intracutaneous tuberculin test positive
8. Accompanying ozena	Klebsiella friedländeri and related organisms
9. Fusospirochetal	Fusobacteria and spirochetes in smears or cultures
10. Parinaud's	Leptothrix; Bacillus tuberculosis; complement fixation and Frei tests positive for virus of venereal lymphogranuloma; agglutination for Past. tularensis positive at times
11. Prexerosis	C. xerosis in bulbar scrapings
12. Syphilitic	Dark field examination shows S. pallida, or Wassermann test positive
13. Accompanying leprosy	Myco. leprae in nodules of eyebrows and conjunctival ulcerations
14. Trachoma	Epithelial cell inclusions present in conjunctival scrapings
15. Inclusion	Epithelial cell inclusions present in conjunctival scrapings
16. Follicular (acute or Béal's)	Mononuclear cells in conjunctival exudate
17. Chronic follicular	Negative
18. Folliculosis	Bacterium granulosis and others of the genus Noguchia (Olitsky, P. K.: Bull. Ophth. Soc. Egypt **26**: 3, 1933. Olitsky, P. K., and Tyler, J. R.: J. Exper. Med. **57**: 229, 1933)
19. Phlyctenular keratoconjunctivitis	Reaction to tuberculin test positive in most cases; occasional acid-fast organisms; Staph. aureus or Haemophilus lacunatus often present (Schieck [51c])
20. Due to virus of herpes simplex, rabies, vaccinia, etc.	Animal inoculation with special technic for identification of virus
21. Molluscum	Elementary bodies in material from nodules
22. Vernal	Eosinophilia in epithelial scrapings
23. Allergic	Eosinophilia in epithelial scrapings
24. Ocular pemphigus	Eosinophilia in epithelial scrapings

* See also Thygeson.[51h]

The most common infection of the lids, the stye, or hordeolum, is usually due to a toxigenic type of Staphylococcus. It is essentially an infection of the glands of Moll or Zeiss. Marginal blepharitis, an infection of the lid border, is of similar causation (Gifford [85]). Anthrax bacilli have been isolated from pustules occurring in a gangrenous lid. The use of specific immune anthrax serum has been found to be valuable in this disease.[51c]

84. von Herrenschwand.[51c] Bayer and von Herrenschwand.[51d]

85. Gifford, S. B.: A Textbook on Ophthalmology, ed. 2, Philadelphia, W. B. Saunders Company, 1941.

VI. BACTERIOLOGIC EXAMINATION OF THE CONJUNCTIVA PRIOR TO INTRAOCULAR OPERATIONS

While a small percentage of normal, noninflamed conjunctivas are sterile, the majority contain a variety of micro-organisms, including Sarcina, diphtheroids, yeasts, molds, staphylococci, Str. viridans, Str. haemolyticus and pneumococci (Keilty [86]). Khorazo and Thompson [8] have pointed out that diphtheroids increase

TABLE 5.—*Organisms Found Most Frequently on Normal Conjunctivas (From Khorazo and Thompson)*

Total Number of Cases in Which Cultures Were Made	Percentage of Cases in Which Each Organism Occurred							
	Staphylococci	Diphtheroids	Str. Viridans	Str. Haemolyticus	Pneumococci	Sarcinas	More Than One Organism	No Growth
1,122	64	36	3.4	1.2	2.6	1	25	17

TABLE 6.—*Results of Bacteriologic Examinations of the Conjunctiva Prior to Intraocular Operation*

Patient, Sex, Age, Date	Clinical History and Diagnosis	Bacteriologic Observations
M. M., ♀, 65, 5/24/35	Cataract, right eye.....	Smear, no organisms, cells or bacteria seen
A. N., ♂, 48, 1/15/37	Bilateral cataract; tabes.....	Culture of material from right eye, no growth; from left, 3 colonies each of Str. viridans and diphtheroids and some of Staph. albus; direct smear, no organisms seen
A. R., ♂, 64, 3/11/38	Mature cataract and conjunctivitis, left eye, sclera acutely injected; patient lost right eye because of infection	Repeated examinations showed 150 colonies of Staph. aureus and 50 of diphtheroids in left eye
A. G., ♀, 67, 4/26/38	Right eye, ciliary injection, anterior chamber cloudy	Repeated examination of right eye showed 40 to 200 colonies of Staph. aureus (hemolytic)
H. R., ♀, 76, 5/16/38	Cataract, right eye.....	Culture, 28 colonies of Staph. albus, 50 colonies of diphtheroids
E. E., ♀, 8, 7/6/38	Mature cataract, left eye.....	Several examinations revealed 20 to 50 colonies of Staph. aureus, a few diphtheroids and hemolytic streptococci
L. K., ♂, 69, 12/23/39	Iritis, left eye; bilateral glaucoma, cataract	Smear, few gram-positive cocci; culture, 80 colonies of Staph. aureus and 25 of diphtheroids; culture, Staph. albus (hemolytic)
L. R., ♀, 36, 6/26/40	Bilateral cataract; myotonia dystrophia	Right eye, several colonies of staphylococci; left eye, similar
C. de L., ♀, 1/14/41	Cataract (mature, senile); iritis, left eye	Smear, negative; culture, Staph. albus (hemolytic)
C. H., ♀, 61	Cataract, right eye; multiple furunculosis of nostrils	Right eye, repeated examinations showed 20 to 25 colonies of Staph. aureus (hemolytic), 5 to 12 colonies of Staph. albus, 25 colonies of diphtheroids
H. S., ♀, 38	Cataract, left eye.....	One colony of Staph. albus; direct smear, no organisms seen
M. D., ♂, 73	Cataract, left eye; diabetes.....	Culture, Staph. albus and diphtheroids, right eye; Staph. albus, left eye

with advancing age and that pneumococci and green streptococci occur most frequently in children under 5 years of age. Pathogenic bacteria, particularly staphylococci, may be present in large numbers without causing clinical evidence of conjunctivitis (table 5). Unless the surgeon takes pains to clean the conjunctiva prior to operation, he may introduce a variety of bacteria into the anterior chamber, where the absence of lysozyme and antibodies will permit their multiplication. It is important to realize that even so-called nonpathogenic bacteria, which appear

86. Keilty, R. A.: The Bacterial Flora of the Normal Conjunctiva with Comparative Nasal Culture Study, Am. J. Ophth. **13**:876, 1930.

on the normal conjunctiva (B. subtilis, P. vulgaris, B. pyocyaneus, Esch. coli, A. faecalis and Bacillus lactis aerogenes) may destroy an eye when they reach the anterior chamber or the vitreous. It is opportune, therefore, to recall the remarks made by Browning [87] in 1914:

> Bacterial infection is one of the causes of failure following the operation of cataract extraction. It was the cause of the loss by removal of about 1 per cent of the eyes operated on for cataract at Moorfields. . . . With modern bacteriological methods, most, if not all of these cases could be avoided, and I think that if all conjunctival sacs were bacteriologically examined before operation there would be fewer post-operative infections, or infections during the operation.

It has been our policy to advise postponement of an operation in the presence of half a dozen or more colonies of hemolytic, toxigenic staphylococci or two or more colonies of hemolytic streptococci, pneumococci or pyocyanic bacilli. Local irrigations with solutions of sulfathiazole and immunization with staphylococcus toxoid and autogenous vaccine are recommended for staphylococcic infections. Sulfanilamide may be used locally for Str. haemolyticus.

Table 6 gives the results of bacteriologic examinations prior to intraocular operations in a series of 12 cases at the Mount Zion Hospital. In 1 case Str. viridans was isolated; in 6 other cases from twenty to two hundred colonies of staphylococci developed on the blood agar plates. The operations were postponed until the apparent or nonapparent infections of the conjunctiva had cleared up and were without unpleasant sequelae.

VII. BACTERIAL INFECTIONS FOLLOWING INTRAOCULAR OPERATIONS

Three patients with serious postoperative infection were examined in our laboratories. The first was a patient who two days after an iridectomy (Dec. 1, 1936) showed signs of endophthalmitis and pus in the anterior chamber due to Str. haemolyticus. This patient was among the first persons in the United States to receive sulfanilamide (then called prontosil). The infection cleared up, but the sight was lost. In a second patient, who had had acute cholecystitis, there developed shortly after a cataract extraction an exudate in the vitreous which may have been embolic from the gallbladder. Culture of material from the eye showed a toxigenic strain of Staph. aureus (hemolytic). After treatment with large doses of staphylococcus antitoxin, the infection was arrested, but the vision did not improve. In a third patient, B. subtilis was isolated from the cornea, which had become infected after a bilateral cataract operation. There were also signs of infection in the anterior chamber (table 7).

Von Herrenschwand [51c] listed the following bacteria as causative agents of postoperative infections: Esch. coli, members of the subtilis group (Bacillus mycoides, Bacillus mesentericus), Pseudomonas fluorescens, staphylococci, pneumococci, streptococci, diphtheria bacilli and influenza bacilli. Occasionally anaerobic toxin-producing bacilli, such as Clostridium tetani and Clostridium welchii, may be incriminated.

Morax [88] isolated in cases of late infection following operation for glaucoma a small gram-negative anaerobic bacillus which was pathogenic in laboratory animals and invaded both the iris and the vitreous of the patient. Kravitz [89] reported post-

87. Browning, S. H.: Post-Operative Complications of Cataract Extraction, Tr. Ophth. Soc. U. Kingdom **34**:58, 1914.

88. Morax, V.: L'infection tardive dans les operations anti-glaucomateuses, Concilium ophth. **13**:99, 1929.

89. Kravitz, D.: Post-Operative Endogenous Infections of the Eyes, Am. J. Ophth. **19**:328, 1936.

operative endogenous gonococcic iridocyclitis in a 78 year old man following cataract operation. The patient had had gonorrheal urethritis sixty years previously, and pus in which gonococci were found developed in the anterior chamber. Fuchs and Verhoeff [90] observed mycotic infections following cataract extractions. The former had a patient in whom the ciliary body and sclera were invaded with actinomyces, while the latter reported an instance in which a fungus produced chronic iridocyclitis, necessitating the enucleation of both eyes.

VIII. BACTERIA IN INFECTIONS OF THE CORNEA

As in conjunctival infections, in corneal infections the etiologic agent varies with the geographic location and the occupation of the patient. Thus, the common cause of serpiginous corneal ulcer (hypopyon ulcer) in the temperate regions of the United States is the pneumococcus. The type distribution according to Cheney [91] is as follows: type IV, 75 per cent, and type III, 25 per cent. In Palestine (Feigenbaum [92]) one sees the Koch-Weeks bacillus (H. influenzae) and in France

TABLE 7.—*Results of Bacteriologic Examinations in Postoperative Infections of the Eye*

Patient, Sex, Date, Age	Clinical History	Bacteriologic Observations	Special Treatment and Clinical Result
G. J., ♂, 12/1/26, 66	Two days after iridectomy, patient showed signs of endophthalmitis, pus in anterior chamber	Smear of pus, gram-positive cocci and diphtheroids; culture, Str. haemolyticus	Sulfanilamide * intramuscularly and by mouth; 20 cc. each of several doses of polyvalent antistreptococcus serum intramuscularly; infection cleared up but sight of eye lost
L. B., ♂, 2/6/39, 60	Cataract, both eyes; acute cholecystitis; during convalescence, exudate developed in vitreous, probably embolic from gallbladder; pain; leukocytosis †	Culture, toxigenic Staph. aureus (hemolytic) and diphtheroids	Staphylococcus antitoxin, 60,000 units intravenously, 60,000 units intramuscularly; vision not improved but infection arrested
S. C., ♀, 6/21/39, 79	Bilateral senile cataract; syphilitic destruction of nasal septum; infection of anterior chamber following extraction of cataract	Direct smear, negative; culture, B. subtilis, 13 colonies	Eye discharging mildly

* This patient was one of the first persons in the United States to be treated with sulfanilamide.
† Staphylococci grown by culture were toxigenic, as shown by production of coagulase, fermentation of mannitol and reaction of crystal violet agar (Fairbrother,[54c] Thygeson,[54d] Thompson and Khorazo [54e]).

the diplobacillus of Morax (H. duplex) and the diplobacillus of Petit (Elliot, Chamberlain and Givner [93]).

Schmelzer [94] reported pneumococci in 60 per cent of such ulcers, streptococci in 20 per cent, the diplobacillus of Morax in 13 per cent, Staph. aureus in 4 per cent and other bacteria in 3 per cent. In China marginal ulcers are caused by Str. haemolyticus, H. influenzae and H. duplex. In the Rhine country (Germany) and in Chicago, the bacillus of zur Nedden, a member of the Friedländer family (Klebsiella), has been described as the cause of a ring ulcer (von Herren-

90. Fuchs, E., and Verhoeff, F. H., cited by von Herrenschwand.[51c]

91. Cheney, R. C.: Types of Pneumococcus Found in Corneal Ulcers, Internat. Cong. Ophth. **1**:378, 1922; abstracted, Zentralbl. f. d. ges. Ophth. **10**:521, 1922; cited by von Herrenschwand.[51c]

92. Feigenbaum, A.: Hornhautkomplikationen bei der in Palästina epidemisch vorkommenden Koch-Weeks Konjunktivitis, Klin. Monatsbl. f. Augenh. **67**:436, 1921.

93. Elliot, A. J.; Chamberlain, W. P., Jr., and Givner, I.: Diplobacillus of Petit in Corneal Ulceration, Arch. Ophth. **25**:280 (Feb.) 1941.

94. Schmelzer, H.: Zur Aetiologie und Therapie des Ulcus serpens, Klin. Monatsbl. f. Augenh. **95**:400, 1935; cited by Pillat.[145f]

schwand [95]). Other organisms which may cause a ring abscess or peripheral annular infiltration of the cornea are: B. subtilis, B. pyocyaneus (Ps. aeruginosa) (Lanou,[96] Lepard [97]), members of the Proteus genus (P. vulgaris) and Pasteurella pestis (Gifford [98]). In Algeria, Toulant and Sarrouy [99] described a type of keratitis, accompanied at times by iritis, cyclitis and descemetitis, occurring during the course of systemic infections with dysentery bacilli. The toxin of the Shiga bacillus was suggested as the causative agent (Dudgeon [100]). In other tropical countries (Strong [51f]) B. pyocyaneus causes severe purulent keratitis as well as conjunctivitis. As a result of vitamin A deficiency, diphtheroid bacilli (Corynebacterium xerosis) multiply on the surface of the cornea (table 8).

The following organisms have also been reported in corneal infections: Myco. tuberculosis,[101] Myco. leprae,[102] C. diphtheriae, Esch. coli, K. pneumoniae, Klebsiella ozaenae and S. pallida (in interstitial keratitis [103]). So-called dendritic ulcer of the cornea (herpetic keratitis) is in all instances due to the virus of herpes simplex.

The bacteriologic diagnosis of infections of the cornea may be used as a guide to therapy. Thus, a serpiginous ulcer due to the pneumococcus is treated with sulfa-

TABLE 8.—*Results of Laboratory Studies in the Principal Types of Corneal Infection*

Clinical Diagnosis	Results of Laboratory Studies
Serpiginous ulcer (hypopyon ulcer)...	Pneumococcus, H. influenzae, H. duplex, Diplobacillus of Petit, Staph. aureus
Marginal ulcer.....	Str. haemolyticus, H. influenzae, H. duplex
Ring ulcer.....	B. neddeni (Klebsiella), Ps. aerogenosa, B. subtilis, P. vulgaris, P. pestis
Keratitis (various types).....	B. dysenteriae, B. pyocyaneus, Gonococcus, Myco. tuberculosis, Myco. leprae, C. diphtheriae, Esch. coli, K. pneumoniae, K. ozaenae, virus of venereal lymphogranuloma
Interstitial (syphilitic) keratitis.....	S. pallida; Wassermann test positive
Trachomatous keratitis (pannus).....	Virus of trachoma (and/or bacterial allergy ?)
Dendritic ulcer (herpetic keratitis)....	Herpes simplex virus
Epidemic keratoconjunctivitis ("shipyard conjunctivitis").....	Specific virus isolated and cultivated by Sanders and Alexander.[122b]
Mycotic and virus infections.....	See text

thiazole or with optochin (ethylhydrocupreine), while one due to the diplobacillus of Morax responds well to zinc sulfate. Successful therapy of trachoma with the sulfonamide compounds has been reported.[104] Arsenical treatment is indicated for interstitial keratitis, which is a manifestation of syphilis.[12]

Infections of the cornea due to fungi and viruses are listed in sections XII and XIII.

95. von Herrenschwand, F.: Zur Bakteriologie und Entstehungsweise des Hornhautrandgeschwüres, Klin. Monatsbl. f. Augenh. **71**:637, 1923.

96. Lanou, W. W.: Bacillus Pyocyaneus Infection of Eye: Report of Two Cases, Am. J. Ophth. **18**:950, 1935; cited by Pillat.[145f]

97. Lepard, C. W.: Corneal Ulcer Due to Bacillus Pyocyaneus, read at the meeting of the Detroit Ophthalmological Society, March 27, 1941; Arch. Ophth. **25**:1079 (June) 1941.

98. Gifford, S. R.: Ring Ulcer of the Cornea, Arch. Ophth. **27**:231 (Feb.) 1942.

99. Toulant, P., and Sarrouy, C.: Les manifestations oculaires des dysenteries bacillaires, Arch. d'opht. **53**:523, 1936.

100. Dudgeon, L. S.: Bacillus dysenteriae (Shiga), in A System of Bacteriology, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, p. 184.

101. Goldenburg, M., and Fabricant, N. D.: The Eye in the Tuberculous Patient, Arch. Ophth. **5**:66 (Jan.) 1931.

102. King, E. F.: The Eye in Leprosy, Brit. J. Ophth. **20**:561, 1936.

103. Lindner.[5] Axenfeld.[51b] von Herrenschwand.[51c]

104. Glover.[1c] Jones.[1f] Landegger.[1g] MacCallan.[11]

IX. BACTERIA AND VIRUSES IN EPIDEMICS OF CONJUNCTIVITIS AND KERATOCONJUNCTIVITIS

Epidemics of conjunctivitis and keratoconjunctivitis due to a variety of bacteria and viruses have been described from time to time in different parts of the world (Kamen,[105] Axenfeld [106]). As pointed out by zur Nedden,[41] these are seldom preceded by epidemics of systemic infectious diseases and are influenced by seasonal and climatic factors as well as by the personal hygiene of the members of the affected community. In Egypt there is a nonvenereal type of gonorrheal ophthalmia in children and adults which is probably transmitted by insects. According to Attiah,[107] Meyerhof [53] and Wilson,[108] it reaches its peak annually during October and November and disappears between January and June. Small epidemics of nonvenereal conjunctivitis due to this diplococcus were described by Lindner [109] among troops during the first World War and by Wu, Teng and Wen [110] among inmates of a poorhouse in China. In the former, a medicine dropper in the hands of an inexperienced medical assistant spread the infection, which originated from the urethra of a soldier. In all, 56 soldiers became infected. In the second epidemic, 60 persons employing common towels and wash basin acquired the disease; of them 10 became blind in both eyes and 11 in one eye.

In New York, in China, in Palestine (Feigenbaum [92]), in France and in Eritrea, Italy (Colomba [111]), the Koch-Weeks bacillus has been found in epidemics of "pink eye." Bengtson [112] reported epidemic and endemic conjunctivitis due to the Koch-Weeks bacillus in the Salton Sea area of California and in the southern states. It is transmitted by means of a small gnat of the species Hippelates. In epidemics of conjunctivitis reported from Russia by Pavlov [113] the incidence of bacteria was as follows: Koch-Weeks bacilli in 6 per cent of the cases, gonococci in 16 per cent, Morax diplobacilli in 30 per cent, staphylococci in 19 per cent and various diplococci in 25 per cent. Oculoglandular tularemia is endemic in some parts of Russia. In Montreal and in Continental Europe, the diplobacillus of Morax produces an occasional epidemic of conjunctivitis; elsewhere the pneumococcus has been incriminated (Mikaeljan [114]).

Barrow [59] described an epidemic, due to B. faecalis alcaligenes, among sailors on a school ship in the London Thames. Among the inclusion viruses which produce endemic and epidemic diseases are those of trachoma, inclusion blennorrhea, swimming bath conjunctivitis and Samoan conjunctivitis.[27] Epidemics of keratoconjunctivitis, probably caused by a virus or viruses of unknown identity, have been

105. Kamen, L.: Zür Aetiologie der epidemischen Bindehautenzündung, Zentralbl. f. Bakt. **25**:449, 1899.

106. Axenfeld.[51a] Axenfeld.[51b]

107. Attiah, M. A. H.: Seasonal Epidemics of Acute Koch-Weeks and Gonococcus Ophthalmias, Bull. Ophth. Soc. Egypt **28**:66, 1936; cited by Pillat.[145f]

108. Wilson, R. P.: Factors in Seasonal Incidence of Acute Ophthalmias, Bull. Ophth. Soc. Egypt **28**:88, 1936; cited by Pillat.[145f]

109. Lindner, K.: Ueber eine endemie von 56 Gonoblennorrhoën, Klin. Monatsbl. f. Augenh. **65**:637, 1920.

110. Wu, C. J.; Teng, C. H., and Wen, C. C.: Gonococcal Ophthalmia: Epidemiological Study, Chinese M. J. **50**:59, 1936; cited by Pillat.[145f]

111. Colomba, N.: Sulla congiuntivite da bacilla di Koch-Weeks in colonia eritrea, Boll. Soc. ital. biol. sper. **11**:60, 1936; cited by Hagedorn.[145l]

112. Bengtson, I. A.: Seasonal Acute Conjunctivitis Occurring in the Southern States, Pub. Health Rep. **48**:917, 1933.

113. Pavlov, N.: Bacteriologic Examination of Conjunctiva in Turkmenistan, Vestnik oftal. **10**:230, 1937; cited by Pillat.[145g]

114. Mikaeljan, R. C.: Studien ueber den Pneumococcus des Auges: I. Ueber Pneumokokkentypen bei einigen Augenerkrankungen, Klin. Monatsbl. f. Augenh. **87**:778, 1931.

described by Wright,[115] in Madras; by Viswalingam,[116] in Malaya; by Kirwan,[117] in Bengal; by Hamilton,[118] in Tasmania; by zur Nedden,[119] in Germany, and by Merrill,[120] in the states of the Pacific coast of the United States. In 1935 Thygeson [121] reported a minor epidemic among students at the University of Iowa of an acute follicular conjunctivitis corresponding in all respects to the type described by Béal in 1907. Since no specific bacteria were isolated and the conjunctival exudates consisted largely of monocytes, the suggestion was made that the etiologic agent might be a virus. In 1939 zur Nedden [119] reported an epidemic of 500 cases of keratoconjunctivitis which was probably due to a virus. The disease was characterized by swelling of the preauricular glands, folliculosis and hemorrhage of the conjunctiva and superficial punctate keratitis. Zur Nedden could not transmit the disease to the cornea of rabbits; neither could he cure it with sulfanilamide. It healed spontaneously in two or three weeks and had certain features in common with nummular keratitis, which possibly is also due to a virus.

Epidemic keratoconjunctivitis ("shipyard conjunctivitis") is probably identical with the infectious disease of the eyes which first reached epidemic proportions several years ago in India, Malaya and Tasmania. It recently broke out among the workers of the shipyards and industrial plants of the Pacific and Atlantic coasts of the United States and was christened "shipyard conjunctivitis." Hogan and Crawford,[122a] of the University of California, recorded that it usually begins as a unilateral, follicular conjunctivitis with edema of the lids, swelling of the caruncle and semilunar fold and a scanty, watery discharge. The second eye becomes involved after a week. The cornea in from seven to twenty-one days shows definite epithelium infiltrates which sometimes become eroded and stained. In most cases the preauricular glands are swollen and tender. Conjunctival smears show a lymphocytic exudate with an occasional large mononuclear cell, and cultures record no significant bacteria. Sanders and Alexander [122b] isolated the specific virus, which is pathogenic for unweaned Swiss white mice when administered by the intranasal, intraperitoneal and intracerebral routes. They maintained the virus by mouse brain passage and proved it to be neurotropic.

The biography of this disease is assumed to be as follows: It was first recognized in Vienna by E. Fuchs, in 1893. It made its appearance in Bombay in 1900-1901 and reached epidemic proportions in Madras, India, in 1920, 1928 and 1930. It traveled to London in 1933, back to India in 1933 and 1934, to Malaya in 1935 to 1938 and to China in 1936. It became widespread in Germany in 1938 to 1940 and in Tasmania in 1941. In the summer of 1941, 10,000 cases were reported in

115. Wright, R. E.: Superficial Punctate Keratitis, Brit. J. Ophth. **14**:257, 1930.

116. Viswalingam, A.: Epidemic Superficial Punctate Keratitis in Malaya, Brit. J. Ophth. **25**:313, 1941.

117. Kirwan, cited by Wright.[115]

118. Hamilton, J. B.: Survey of Superficial Punctate Keratitis in Tasmania with the Record of a Mild Epidemic, Brit. J. Ophth. **25**:1, 1941.

119. zur Nedden, M.: Beobachtungen an 500 Fällen von Kerato-Conjunctivitis epidemica, Klin. Monatsbl. f. Augenh. **105**:424, 1940.

120. Merrill, H. G.: Epidemic Kerato-Conjunctivitis Diversiformis, Am. J. Ophth. **19**: 1007, 1936.

121. Thygeson, P.: A Papillary Type of Béal's Conjunctivitis, Am. J. Ophth. **21**:1017, 1938.

122a. Hogan, M. J., and Crawford, J. W.: Epidemic Keratoconjunctivitis (Superficial Punctate Keratitis, Keratitis Subepithelialis, Keratitis Maculosa, Keratitis Nummularis) with a Review of the Literature and a Report of 125 Cases, Am. J. Ophth. **25**:1059, 1942.

122b. Sanders, M., and Alexander, R. C.: Epidemic Keratoconjunctivitis: I. Isolation and Identification of a Filterable Virus, J. Exper. Med. **77**:71, 1943.

Oahu, Territory of Hawaii.[122c] It reached the Veteran's Hospital, San Fernando, Calif., in 1941 and spread to the shipyards of the Pacific coast the same year. Outbreaks occurred in the industrial plants of the Atlantic seaboard early in 1942.

X. INFECTIONS OF THE LACRIMAL APPARATUS[123]

Although the mucous membrane of the lacrimal duct is continuous with that of the conjunctiva, nevertheless, because of the downward drainage of the tears with their content of bactericidal substances and lysozyme, organisms such as the Morax bacillus, the Koch-Weeks bacillus and the gonococcus, which infect the conjunctiva, rarely, if ever, produce disease in the tear duct. Dacryocystitis usually arises as an extension of an infection in one of the sinuses, such as the ethmoid, frontal or maxillary, or from an obstruction of the duct by a foreign body or a mycotic concretion. Streptothrix is the fungus most commonly involved. Actinomyces has been incriminated by Charlon.[124] As a result of infection of the tear duct there may develop so-called "lacrimal conjunctivitis."

The organisms which produce disease of the lacrimal apparatus usually have their origin in the respiratory or intestinal tract. In cases of acute infection one finds pneumococci, staphylococci, streptococci, influenza and Friedländer bacilli, M. catarrhalis, the fusobacteria and oral spirochetes, the bacillus of glanders (M. mallei), P. vulgaris, B. pyocyaneus and B. mesentericus. Members of the Bacteroides genus (Bacillus funduliformis, etc.) have been isolated in cases of gangrene and phlegmon. In cases of chronic infection pneumococci, streptococci, staphylococci, influenza bacilli, Friedländer bacilli and diphtheroids may be isolated. Occasionally it is possible to find tubercle bacilli in the discharges of tuberculous dacryocystitis. Guinea pig inoculation should therefore be resorted to.

A variety of molds and higher bacteria have been reported, which are listed in section XII.

XI. BACTERIA IN IRITIS, UVEITIS, IRIDOCYCLITIS, CHOROIDITIS AND PANOPHTHALMITIS

While most of the diseases of the conjunctiva and cornea may be characterized as local infections, usually caused by bacteria or viruses which are regarded as epithelial cell parasites, the eye shares with other organs of the body the burden of a generalized invasion, or toxemia. Thus, in cases of sepsis due to Str. haemolyticus, Meningococcus (Reese,[125] Dunphy,[126] Eagleton[127]), Esch. coli (Steiff[128]), Staph. aureus, B. pyocyaneus, Eberthella typhosa, Pneumococcus (Hulka[129]), Past. pestis, etc., one may observe not only conjunctivitis or keratitis but, at times,

122c. Epidemic Virus Conjunctivitis, editorial, J. A. M. A. **118**:460 (Feb. 7) 1942.

123. For literature on dacryocystitis, see: Fahmy, A. Y.: Pathology of Dacryocystitis, Bull. Ophth. Soc. Egypt **27**:41, 1934; cited by Pillat.[145e] Axenfeld.[51a] Axenfeld.[51b] von Herrenschwand.[51c]

124. Charlon, A.: Concretions in a Lacrimal Canaliculus Caused by Actinomyces, Brit. J. Ophth. **19**:385, 1935.

125. Reese, F. M.: Meningococcus Conjunctivitis Followed by Septicemia and Beginning Meningitis, Am. J. Ophth. **19**:780, 1936.

126. Dunphy, E. B.: Ocular Complications of Cerebrospinal Meningitis, Arch. Ophth. **15**:118 (Jan.) 1936.

127. Eagleton, W. P.: Suggestions for the Prevention of Ocular and Aural Sequelae of Meningococcic Meningitis, Arch. Ophth. **18**:46 (July) 1937.

128. Steiff, B.: Klinische und pathologisch-anatomische Untersuchungen einer Panophthalmie bei Kolibazillose, Klin. Monatsbl. f. Augenh. **95**:107, 1935; cited by Pillat.[145f]

129. Hulka, J. H.: Metastatic Pneumococcic Uveoscleritis Following Pneumonia, Arch. Ophth. **17**:127 (Jan.) 1937.

metastatic iritis, uveitis, iridocyclitis or panophthalmitis. Some of these lesions (uveitis, iritis) may also be seen during the course of systemic infection with the gonococcus, S. pallida or Myco. tuberculosis (Goldenburg and Fabricant [101]).

In the present investigation (table 9) there was an example of invasion of the ocular tissues from a distant focus in the body in a patient with bacterial endocarditis. Several days before his death, a severe infection of the eye developed, with rupture of the cornea. After enucleation and section, the eye showed evidence of subacute iridocyclitis, choroiditis and suppurative panophthalmitis due to Str. viridans. The same organism was isolated from the heart's blood at autopsy. A similar course was described by Caramazza [130] in a 25 year old rheumatic patient in whom neuroretinitis developed and death occurred from generalized sepsis. Two hours before death Str. viridans was recovered from the aqueous humor. Additional cases have been reported, in which invasion of the ocular tissues followed pneumonia, septic abortion, etc. (Ring [131]).

TABLE 9.—*Results of Bacteriologic Examinations in Infections of the Cornea and Orbit*

Patient, Sex, Date, Age	Clinical History	Bacteriologic Observations	Special Treatment and Clinical Results
S., ♀, 4/2/29, 42	Progressive opacity of cornea of right eye; appearance like mother-of-pearl; diminution of vision *	Fungus resembling Grubyella ferruginea (see text)	None; unsatisfactory
F. S., ♂, 4/21/35, 13	Patient struck with stick in left eye while playing; acute suppurative ethmoiditis and maxillary sinusitis developed; acute suppurative orbital and periorbital abscess of left eye; acute suppurative meningitis and abscess of left frontal lobe of brain; septicemia; Str. viridans	Culture, Staph. aureus, Str. viridans, Fusobacterium, B. subtilis; anaerobic culture, Fusobacterium; blood culture, Str. viridans	Patient died 4/23/35
L. L., ♂, 1/15/31, 21	A piece of steel entered left eye, which had to be enucleated; later right eye showed diminution of vision	Enucleated eye † cultured on Löwenstein's medium and material injected into guinea pig; no evidence of tubercle bacilli in eye or in patient's blood	.....
A. R., ♂, 5/30/31, 63	Panophthalmitis of right eye; purulent conjunctivitis; sclera and bulbar conjunctiva congested	Culture, Staph. aureus (hemolytic) and diphtheroids; blood culture, negative	Enucleation of right eye
C. W., ♂, 11/14/40, 54	Acute bacterial endocarditis; syphilis; metastatic, suppurative, panophthalmitis with spontaneous rupture of cornea	Blood culture, Str. viridans; culture of enucleated eye at autopsy, Str. viridans	Sulfapyridine and sulfathiazole; patient died 11/15/40

* This woman was a patient of Dr. Meyer Wiener, St. Louis.
† On section this eye showed subacute iridocyclitis and choroiditis.

British and French investigators (Dudgeon,[100] Toulant and Sarrouy [99]), who observed iridocyclitis, uveitis and conjunctivitis in patients with bacillary dysentery, have suggested that the bacterial toxin produced the injury, since cultural isolation was not successful. Deep-seated infections of the eye may result from involvement of the adjacent sinuses or the bones of the orbit or from focal infection. The latter implies an area of mild or chronic infection which may give rise to symptoms in a distant region. Rosenow's [132] theory that various strains of micro-organisms have the capacity to localize selectively in the iris or the uvea has not found adequate support in either the clinical or the experimental literature (Zanettin [133]). The

130. Caramazza, F.: Neuroretinite settica da "Streptococcus viridans" anemolitico de Schottmüller, Rassegna ital. d'ottal. **4**:19, 1935; cited by Pillat.[145e]

131. Ring, G. O.: Ocular Disease, Notably of the Uveal Tract, Induced by Streptococcus Viridans Infection, Zentralbl. f. d. ges. Ophth. **20**:401, 1929.

132. Rosenow, E. C.: Elective Localization of Bacteria in the Animal Body, in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 576.

133. Zanettin, G.: Focal Infection and Ocular Diseases, Ann. di ottal. e clin. ocul. **62**:588, 695 and 786, 1934; abstracted, Arch. Ophth. **14**:496 (Sept.) 1935.

role of bacterial allergens and of circulating, diffusible toxins must not be overlooked. The usual sites of focal infection are the teeth, tonsils, sinuses, prostate, urinary tract and gallbladder. Lesions of the inner structures of the eye may result from direct infection by way of the blood stream, from systemic intoxication with toxins in the blood stream or from an allergic sensitization due to the liberation of foreign protein at the site of infection (Duke-Elder [3]).

Invasion of the inner structures of the eye with mixed aerobic and anaerobic flora, including fusobacteria, Cl. welchii and Cl. tetani, have been observed after trauma. In the present series I examined a boy, aged 13, who was struck with a stick while playing. Suppurative ethmoiditis, maxillary sinusitis and an orbital and periorbital abscess of the left eye developed. Later he showed signs of acute suppurative meningitis and abscess of the left frontal lobe of the brain, from which he died. Fusobacteria, Staph. aureus, Str. viridans and B. subtilis were recovered from the eye, while the blood culture showed Str. viridans. Kluever and O'Brien [134] reported an infection with Cl. welchii which followed injury from a foreign body. Fulminating panophthalmitis with gas in the anterior chamber resulted, requiring evisceration of the eye. Other anaerobic organisms, including Clostridium botulinum and bacteria of the gas gangrene group, may be incriminated (Jacqueau,[135] Swab [136]).

I have been unable to confirm the theory of Löwenstein [137] and Meller [138] that sympathetic ophthalmia is essentially a tuberculous uveitis occurring in a person whose eye is injured at a time when he has bacillemia due to Myco. tuberculosis. With the collaboration of Dr. Otto Barkan, we made cultures on Löwenstein's medium of the blood of a patient and of one of his eyes which had been enucleated because sympathetic ophthalmia developed in the opposite eye after an injury. The cultures, as well as the results of guinea pig inoculations, were negative for tubercle bacilli. Similar conclusions have been reached by Gasteiger [139] and others.

In more recent years attention has been given to the ocular complications of Malta fever, due to Br. melitensis (Green,[22] Madijewskaja,[140] Nikolaeva [23]). Recurrent iritis, uveitis and papilledema have been observed. Nikolaeva [23] described clouding of the cornea, the anterior chamber and the vitreous. In 1 case there were observed at autopsy a marked corneal infiltration with destruction of Bowman's membrane, detachment of the retina and giant cell infiltration in various areas with mild cellular infiltration of the optic disk. The iris and the ciliary body showed perivascular infiltration. Green [22] listed among the ocular manifestations of brucellosis, corneal ulcer, optic neuritis, atrophy of the optic nerve, papilledema and constriction of the field, iritis, iridocyclitis, hemorrhages

134. Kluever, H. C., and O'Brien, C. S.: Panophthalmitis Due to Clostridium Welchii, Arch. Ophth. **15**:1088 (June) 1936.

135. Jacqueau: Tétanos par corps étranger intra-oculaire, Bull. Soc. d'opht. de Paris **6**:452, 1935; cited by Pillat.[145f]

136. Swab, C. M.: The Histological Background of the Ocular Syndrome in Botulism, Arch. Ophth. **3**:437 (April) 1930.

137. Löwenstein, E.: Die Züchtung der Tuberkelbazillen aus dem strömenden Blute, Zentralbl. f. Bakt. **120**:127, 1931; Die sympathische Ophthalmie: Ein Einzelfall das Gesetzes der sympathischen Entzündungen, Beitr. z. Klin. d. Tuberk. **82**:770, 1933.

138. Meller, J.: Ueber Bazillämie und sympathische Ophthalmie, Ztschr. f. Augenh. **79**:110, 1932; Die sympathische Ophthalmie durch Gewebkultur aus dem sympathisierenden Auge als eine echte bazilläre Erkrankung nachgewiesen, ibid. **79**:95, 1932.

139. Gasteiger: Ueber den Wert der Blutkulturen nach Löwenstein für die Diagnose von Augenkrankheiten, Klin. Monatsbl. f. Augenh. **98**:367, 1937; cited by Pillat.[145g]

140. Madijewskaja, E., cited by Pillat,[145f] p. 47.

into the retina and the vitreous with secondary glaucoma, palsies of the extraocular muscles, neuroretinitis, choroiditis, central retinochoroiditis and panophthalmitis with bulbar atrophy. As noted in section II, on technical procedures, the agglutination test is helpful in the diagnosis.

Several cases of oculoglandular tularemia in human beings have been reported in the American and in the European literature (Vail,[15b] Simpson,[16] Dvorak,[141] Pillat and David,[142] Pfingst [18]). The agglutination test with the blood serum of the patient is usually positive after the first week of infection. While the titer may be 1 : 2,000 or over, it is generally much lower—in the neighborhood of 1 : 160. Inoculation of a guinea pig with material obtained from the conjunctiva may cause the death of the animal. It has recently been shown that Parinaud's conjunctivitis may, at times, be due to infection with Past. tularensis. As indicated, there are other etiologic agents, including the bacillus of tuberculosis, Leptothrix and the virus of lymphogranuloma venereum.

Infections of the eye due to organisms of the Leptospira group (L. icterohaemorrhagica and L. canicola) have recently been reported. Legras and Wolters,[24] in Holland, saw a woman with choroiditis and iritis who had acquired the disease from a dog which had Weil's disease as a result of drinking water from a ditch in which rats had been found. The patient's blood gave a positive agglutination reaction in 1 : 100 dilution with an emulsion of L. canicola. During the course of her convalescence the titer reached 1 : 3,000. Other spiral organisms which may cause ocular lesions with systemic invasion are Spirillum minus [142a] and Spirillum morsus muris.[142b] The former is the cause of ratbite fever. The latter has been reported as the cause of optic neuritis in Brazil.

The ocular manifestations of virus diseases are protean. Macnie [31] has observed that in patients with lymphogranuloma venereum, conjunctivitis, retinal hemorrhages, episcleritis and peripapillary edema may develop, as well as involvement of the retinal vessels. The virus may be demonstrated in the conjunctival secretion or in bits of excised conjunctival tissue. Thirty patients with keratoconjunctivitis and uveitis all reacted positively to the Frei test. Infected aqueous humor may produce characteristic meningoencephalitis in white mice (von Haam and Hartwell [143]). During the course of epidemic encephalitis the following ocular manifestations may occur: ptosis, blepharospasm, diplopia, strabismus, nystagmus and papilledema. In the course of meningotyphus of swine herders (maladie de Bouchet) Babel [144] observed bilateral fibrinous iritis.

XII. MYCOTIC INFECTIONS OF THE EYE [145]

Since the conjunctiva and cornea are exposed surfaces of the body, it is not surprising that a variety of higher bacteria, yeasts and molds may be found there

141. Dvorak, T. G.: Oculoglandular Tularemia, Am. J. Ophth. **15**:112, 1932.

142. Pillat, A., and David, H.: Ueber Tularämie beim Menschen in Österreich, Ztschr. f. Augenh. **91**:1, 1937.

142a. Tassman, I. S.: The Eye Manifestations of Internal Diseases, St. Louis, C. V. Mosby Company, 1942.

142b. Alvari, M. E.: Brazilian Ophthalmology, Am. J. Ophth. **26**:474, 1943.

143. von Haam, E., and Hartwell, R.: Experimental Conjunctivitis Caused by Virus of Lymphogranuloma Inguinale, J. Trop. Med. **39**:190, 1936.

144. Babel, J.: Ueber Augensymptome bei der sogenannten Schweinehirtenkrankheit (Maladie des porchers), Ophthalmologica **96**:159, 1938.

145. For literature on mycotic infections of the eye, see: (*a*) Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935. (*b*) Colomba, N., cited by Pillat.[145f] (*c*) Anderson, W. B., and Byrnes, T. H.: A Case of Rhinosporidium of the Conjunctiva, Am. J. Ophth. **22**:1383, 1939. (*d*) Borsotti, J.: Contributo allo studio dell'oculotropismo sperimentale,

under normal conditions. Infection may occur as a result of malnutrition, injury with a foreign body or extension from the scalp, face or eyelids. Fazakas [146] has isolated fungi from 56 per cent of normal conjunctivas and from 37 per cent of diseased ones and identified no less than forty-two different types from a series of 493 patients. He called attention to the possibility that fungi may contribute to the inflammatory reactions in disease processes.

Since mycology has developed into a more or less independent science, the clinical pathologist will find it best to refer to standard works, such as those of Dodge,[145a] Henrici [145j] and Lewis and Hopper,[147] and to send cultures to the leading mycologists, including Dodge, Weidman, Stevenson and Hopkins, for identification or confirmation.

In the following tabulations are listed some of the more common fungi which have been reported in cases of infection of the conjunctiva, cornea and lacrimal apparatus:

A. Fungi Which Have Been Frequently Isolated from the Conjunctiva *

Achorion schoenleini
Acrothecium hominis Oláh
Actinomyces berardinisi
Aspergillus fumigatus
Blastomyces (several types)
Leptothrix buccalis
Monilia albicans
Mucor (several types)
Nocardia dassonvillei
Penicillium glaucum
Rhinosporidium seeberi
Sporotrichum schenki
Sporotrichum beurmanni
Streptothrix aurea (Nocardia aurea)
Streptothrix foersteri
Trichophyton (several types)
Yeasts (several types)

B. Fungi Which Have Been Isolated from the Eyelids

Achorion schoenleini
Actinomyces (several types)
Monilia albicans
Microsporum felineum
Trichophyton (several types)
Streptothrix zur Nedden
Trichophyton tonsurans
Trichophyton asteroides
Acrothecium hominis Oláh
Acrostalagmus cinnabararinus Corda

C. Fungi Which Have Been Isolated from the Cornea

Actinomyces cerebriformis
Actinomyces luteolus (Nocardia luteola)
Actinomyces radiatus
Acrostalagmus cinnabarinus
Aspergillus flavus
Blastomyces (various types)
Aspergillus fumigatus
Cephalosporium Serra
Cryptococcus cavarae
Grubyella ferruginea
Monilia cornealis
Mucor cornealis
Mucor mucedo
Protemyces cornealis
Scopulariopsis koningi
Sporotrichum jeanselmei
Streptothrix (several types)
Trichosporium graphii
Verticillium rubrum

D. Fungi Which Have Been Isolated from the Tear Sac

Streptothrix zur Nedden
Leptothrix
Sporotrichum beurmanni
Sporotrichum councilmani
Sporotrichum schenki
Streptothrix foersteri
Scopulariopsis blochi

* Nomenclature according to Dodge.

Boll. d'ocul. **15**:716, 1936; cited by Pillat.[145f] (*e*) Pillat, A.: Bakteriologie, Parasitologie, Immunitätsforschung und Vergiftungen, Ztschr. f. Augenh. **89**:158, 1936; (*f*) **92**:42, 1937; (*g*) **95**:64, 1938. (*h*) Hagedorn, A.: Augenlider, Ophthalmologica **96**:276, 1938; (*i*) Bindehaut, ibid. **97**:28, 1939. (*j*) Henrici, A. T.: Molds, Yeasts and Actinomycetes, New York, John Wiley & Sons, Inc., 1930. (*k*) Fazakas, A.: Fungi Grown from Conjunctiva, Cornea and Lacrimal Passages, Arch. f. Ophth. **133**:461, 1935; abstracted, Arch. Ophth. **15**:329 (Feb.) 1936; (*l*) Durch Acrothecium hominis Oláh bedingte Konjunctivitis Meibomiana, Klin. Monatsbl. f. Augenh. **96**:401, 1936; Die von Bindehaut Hornhaut, Lidrand und Tränenwege zu züchtenden Schimmel- und Spaltpile, ibid. **96**:399, 1936; Pilze in den Tränenwegen, an den Lidern und Lidrändern, ibid. **96**:106, 1937; Ueber Pilzerkrankungen der Hornhaut, ibid. **106**:56, 1941; cited by Pillat (*f* and *g*). (*m*) Axenfeld.[51a] (*n*) von Herrenschwand.[51c]

146. Fazakas.[145k] Fazakas.[145l]

(Footnotes continued on next page)

While working in the Department of Ophthalmology, Washington University School of Medicine, St. Louis, in 1929, I examined a patient of Dr. Meyer Wiener, who had a progressive mother-of-pearl-like opacity of the cornea of one eye. In scrapings of the lesion a fungus of the genus Achorion, resembling Grubyella ferruginea (Dodge [145a]), was isolated. On Sabouraud medium and on blood agar plates, the filaments were golden yellow. A port wine pigment was diffused throughout the medium. Inoculated into the anterior chamber of a rhesus monkey (Macaca mulatta), it caused keratitis, congestion of the scleral vessels and edema of the lacrimal caruncle. The inflammation subsided after three or four days, but a considerable amount of conjunctival and pericorneal congestion remained. After two weeks, the cornea was still hazy, with a dense white opacity in the lower quadrant and a posterior synechia. The pupil was irregular, and there was a definite iritis.

Dr. Fred Weidman, of the Laboratory for Dermatological Research of the University of Pennsylvania School of Medicine, Philadelphia, aided in the identification of the fungus and sent the following notes: "Dextrose agar colonies (eighteen days old) are 1 cm. in diameter and heaped up 6 to 8 mm. above the level of the substrate. They are sharply marginated, the margins rising abruptly over the substrate. The surface is lumpy, gray-white in the younger, more advancing parts and rich orange-yellow in the older. In the gray parts, the texture of the colony appears moist where the layer of duvet is so thin as to be translucent, but elsewhere it is finely duveteuse. In the yellow parts it is finely granular. The underlying medium is not discolored. The hyphae of the colony penetrate for only short distances into the substrate. Material from ten week old dextrose agar cultures shows no highly specialized fructifications such as might be expected from so highly colored a colony. There are a few chlamydospores and two types of hyphae, thinner and coarser. The chlamydospores are large, measuring up to 25 microns in diameter, and have a thick shell and more or less granular interiors. They stain diffusely brown, and the granulations in their interiors are partly dark brown. No sclerosis or asci were seen."

XIII. VIRUS INFECTIONS OF THE EYE

The diagnosis of virus infection of the eye with the exception of infection due to an inclusion virus (inclusion blennorrhea, swimming bath conjunctivitis, trachoma, etc.) and herpes simplex, requires a technic which is too elaborate for the average clinical laboratory. Standard works, such as those of Hyde and Gardner [148] and the symposium of the Harvard School of Public Health,[149] may be consulted for details of methods.

Except for the inclusion viruses and the virus of "shipyard conjunctivitis" (epidemic keratoconjunctivitis), which have a special affinity for the conjunctiva and cornea, those listed hereafter produce a systemic infection in which the eyes may participate. The so-called dendritic ulcer of the cornea is due to the virus of herpes simplex, which causes herpes of the lips. Vitamin A deficiency may play an ancillary role. Several epidemics of keratoconjunctivitis in which viruses probably have played an etiologic role have been referred to (section IX).

147. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1939.

148. Hyde, R. R., and Gardner, R. E.: Laboratory Outline in Filterable Viruses, New York, The Macmillan Company, 1937.

149. Virus and Rickettsial Diseases, Symposium, Cambridge, Mass., Harvard University Press, 1940. Thygeson, P.: Virus and Virus Diseases of Eye, Arch. Ophth. **29**:285 (Feb.); 635 (April) 1943.

Some of the viruses which are known to affect the conjunctiva and/or the cornea are the inclusion viruses of trachoma, inclusion blennorrhea (Julianelle[27]), swimming bath conjunctivitis (Rohrschneider[150]) and epitheliosis desquamativa (conjunctivitis of Samoa) (Julianelle[27]), and the viruses of herpes simplex (Noe,[151] Friedenwald,[152] Velhagen,[153] Gundersen[154]; herpes zoster and vaccinia (Perdrau[155]); rabies (Levaditi and Schoen[156]); measles and poliomyelitis (Bruce[157]); encephalitis (Kennedy[158]); mumps (Danielson[159]); varicella (Pickard[160]); pappataci fever (Rameev[161]); molluscum contagiosum, yellow fever[155]; lymphogranuloma venereum (Appelmans,[32] Levaditi and associates,[162] Meyer and Reber[163]), and meningotyphus of swineherders (*maladie des porchers, maladie de Bouchet*) (Babel[144]). Among the rickettsial diseases which may affect the eyes are typhus fever and tsutsugamushi fever.[164]

2200 Post Street.

150. Rohrschneider, W.: Die Schwimmbadkonjunktivitis und ihr endemisches Auftreten in Berlin von 1919 bis 1925, Klin. Monatsbl. f. Augenh. **76**:619, 1926.

151. Noe, C. A.: Herpes Simplex of the Cornea, J. Iowa M. Soc. **29**:400, 1939.

152. Friedenwald, J.: Studies of Virus of Herpes Simplex, Arch. Ophth. **52**:105, 1923.

153. Velhagen, K.: Experimente mit Herpesvirus zur Frage der Infektionsüberstragung von Bulbus zu Bulbus, Arch. f. Ophth. **119**:324, 1927.

154. Gundersen, T.: Herpes Corneae, Arch. Ophth. **15**:225 (Feb.) 1936.

155. Perdrau, J. P.: Affections of the Eye Due to Viruses, Lancet **1**:975, 1931.

156. Levaditi, C., and Schoen, R.: Les corps de Negri dans le cytoplasme des épitheliums de la cornée, Ann. Inst. Pasteur, 1935, supp., p. 69; cited by Pillat.[145f]

157. Bruce, G. M.: Virus Diseases and the Eye in Childhood, J. Pediat. **18**:592, 1941.

158. Kennedy, F.: Ocular Disturbances in Epidemic Encephalitis, Arch. Ophth. **1**:346 (March) 1929; abstracted, J. Nerv. & Ment. Dis. **69**:194, 1929.

159. Danielson, R. W., and Long, J. C.: Keratitis Due to Mumps, Am. J. Ophth. **24**:655, 1941.

160. Pickard, R.: Varicella of the Cornea, Brit. J. Ophth. **20**:15, 1936.

161. Rameev, R. S.: Ocular Complications of Pappataci Fever, Soviet. vestnik oftal. **9**:347, 1936; cited by Pillat.[145f]

162. Levaditi, C.; Bollack, J.; Basch, G., and Desvignes, P.: Conjunctivite avec adénopathie due au virus de la maladie de Nicolas-Favre, Bull. Soc. franç. de dermat. et syph. **43**:1238, 1936; cited by Pillat.[145f] Levaditi, C.; Schoen, R., and Reinie, L.: Reproduction expérimentale de la conjonctivite lymphogranulomateuse (maladie de nicoles et Favre) chez le chimpanzé, Compt. rend. Acad. d. sc. **203**:828, 1936; cited by Pillat.[145f]

163. Meyer, G. P., and Reber, J.: Corneal Ulcer Associated with Lymphogranuloma Venereum, Am. J. Ophth. **24**:161, 1941.

164. Kawamura, R.: Studies on Tsutsugamushi Disease, edited by N. C. Foot and S. Tashiro, Medical Bulletin, College of Medicine, University of Cincinnati, Cincinnati, Spokesman Publishing Co., 1926, vol. 4, special nos. 1 and 2.

Correspondence

CONVERSION FORMULA FOR SNELLEN SYMBOLS

To the Editor:—Various attempts have been made to find a suitable formula for conversion of conventional Snellen symbols into less conventional equivalents. An acceptable method and its accompanying rationale are here briefly outlined.

With, for example, Sn 20/25 (binocular requirement for Naval inductees), the proper procedure is illustrated in the following equation:

$$20/25 = x/20$$
$$25x = 400$$
$$x = 16$$

or

$$20:25::x:20$$
$$25x = 400$$
$$x = 16$$

Therefore 16/20 is the equivalent of 20/25. Conversely, with Sn 16/20:

$$16/20 = 20/x$$
$$16x = 400$$
$$x = 25$$

or

$$16:20::20:x$$
$$16x = 400$$
$$x = 25$$

Therefore 20/25 is the equivalent of 16/20.

It is evident from the foregoing that, as defined, these Snellen notations represent a relation or ratio of two numerical values of the same kind and denote one or more aliquot parts of a unit, while expressing at the same time a definite proportion; in short, each by its very nature connotes a true fraction. I have on several occasions demonstrated the validity of such a premise. Hence this conversion formula has a sound basis in fact, and, indeed, lends strong support to the solution previously proposed for the evaluation of the Snellen symbol.

346 State Street.

J. A. C. Gabriels, M.D., Albany, N. Y.

News and Notes

EDITED BY DR. W. L. BENEDICT

Reprints Requested.—Word has been received from Lieut. Col. Derrick Vail, who is the ophthalmic consultant to American forces in England, that he would like to receive reprints of articles written by his colleagues in this country. These may be sent to Lieut. Col. Derrick T. Vail, Office of the Chief Surgeon, A. P. O. 871, New York, N. Y. These are not only for his benefit but for that of the British ophthalmologists with whom he is in contact.

PERSONAL NEWS

Dr. Robert K. Lambert Receives Appointment.—Dr. Robert K. Lambert has been appointed ophthalmic surgeon to the Mount Sinai Hospital, New York.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Aqueous Humor

A STUDY OF AQUEOUS HUMOR AS AN AID TO UNDERSTANDING UVEITIS AND CERTAIN RELATED CONDITIONS. R. IRVINE, A. R. IRVINE and M. D. IRVINE, Am. J. Ophth. **25:** 150 (Feb.) 1942.

The authors aspirated aqueous from the eyes of 44 patients with uveitis, glaucoma and separation of the retina and from the eyes of 12 rabbits with experimentally induced sclerokeratitis. Various chemical determinations were carried out, but the data given are too limited for final conclusions, this being a preliminary report.

W. S. REESE.

Conjunctiva

THE ROLE OF THE MEIBOMIAN GLANDS IN RECURRENT CONJUNCTIVITIS. R. G. SCOBEE, Am. J. Ophth. **25:** 184 (Feb.) 1942.

Scobee discusses the anatomy, physiology and pathology of the meibomian glands and reports experiments in 18 cases. He reaches the following conclusions:

"(1) It is a short, direct route from acute staphylococcal conjunctival infection to meibomian glandular involvement; this almost invariably happens.

"(2) Staphylococci in the meibomian glands play a prominent part in recurrent conjunctivitis; if they are not eliminated from the glands, they eventually lead to chronic conjunctivitis.

"(3) Lid massage, repeated weekly, in addition to continued use of antiseptic eye drops for four to six weeks following the cessation of an acute conjunctivitis, will accomplish the removal of staphylococci from the meibomian glands.

"(4) Addition of adrenalin [epinephrine hydrochloride] to antiseptic eye drops promotes drainage of the meibomian glands.

"(5) Regularly repeated lid massage gives great symptomatic relief to patients with stubborn chronic conjunctivitis."

W. S. REESE.

Congenital Anomalies

A CASE OF DEFICIENCY OF THE MALAR BONES WITH DEFECT OF THE LOWER LIDS. I. L. JOHNSTONE, Brit. J. Ophth. **27:** 21 (Jan.) 1943.

Johnstone's patient was a boy aged 14. There is no description of the case other than the statement that the patient presented exactly the condition described by Ida Mann at the Oxford Ophthalmological Congress in July 1942. An accompanying photograph confirms this statement. One roentgenogram shows that the zygomas were poorly developed and a view of the base of the skull that they came to a point. The poor development is also seen in the "nose-chin" view.

The right eye was operated on first. The normal outer third of the lower lid and a triangle of tissue including the fibrous band was excised with the hope of raising the notch up to the outer canthus. The effect, however, was to pull the upper eyelid down. Later a sliding graft from the cheek gave slight improvement.

When the left eye was operated on a pedicle graft from the upper lid was inserted into the lower lid. Only the fibrous band and notch were removed. The result was fairly satisfactory.

W. ZENTMAYER.

Cornea and Sclera

SUPERFICIAL VASCULARIZATION OF CORNEA: RESULTS OF RIBOFLAVIN THERAPY. H. R. SANSTEAD, Pub. Health Rep. **57:** 1821 (Nov. 27) 1942.

Sanstead discusses the prevalence of superficial vascularization of the cornea in groups of school children, youths and adults of various ages and the effect that riboflavin therapy had on the condition. The 366 persons examined were residents of Hagerstown, Md., or its immediate vicinity. Fifty-two of those examined were given riboflavin. From 80 to 95 per cent had some degree of corneal invasion by capillaries. Corneal invasion was relatively more frequent and more severe among the older persons. Of the parochial school children 67 per cent and of the National Youth Administration youths 17 per cent had only two quadrants affected, and for the older subjects the figure was 30 per cent. The corneal vascularization of 15 older subjects who had received 615 to 1,630 mg. of riboflavin during at least sixty days was not significantly different from that of 15 control persons of similar age. Likewise, the therapeutic effect was similar in the 11 parochial school children given 5 mg. of riboflavin twice daily for forty-nine days or 10 mg. daily and in the 11 controls. It appears doubtful that superficial corneal vascularization is a diagnostic sign of riboflavin deficiency.

J. A. M. A. (W. ZENTMAYER).

A CASE OF MUSTARD GAS KERATITIS UNDER CONSTANT OBSERVATION FOR A PERIOD OF TWENTY YEARS. T. L. DE COURCY, Brit. J. Ophth. **27:** 54 (Feb.) 1943.

The patient, a man aged 62, had acute gas poisoning from a bursting shell in May 1918. He returned to service with some improvement of sight. In 1922 there was scarring of the cornea below the pupil. From 1925 he had recurring yearly attacks of ulceration of the corneas leading to marked scarring with increasing loss of vision. In 1924 it was noted that the corneas were anesthetic. About 1920 cholesterol crystals were seen in abundance in the substance of the corneas. Single blood vessels encroached on the corneas. Bullae were of frequent occurrence. Of late contact lenses have greatly improved the visual acuity, which is now 6/9 in the right eye. The treatment over the intervening years is recorded in detail. Among the procedures of more or less value were roentgen therapy, short wave diathermy, peritomy and use of contact lenses.

W. ZENTMAYER.

General Diseases

INTESTINAL AUTOINTOXICATION AS CAUSE OF CHRONIC BLEPHAROCONJUNCTIVITIS. V. L. SZERDAHELYI, Gastroenterologia **67:** 147, 1942.

Szerdahelyi cites reports from the literature which suggest that intoxication of intestinal origin plays a pathogenic role in many general symptoms and in disorders of the type of uremia, cirrhosis of the liver, pernicious anemia and other anemias, ileus, chronic dysentery, chronic arthritis, many forms of neuritis, vasomotor rhinopathy, certain allergic manifestations, eczemas, bronchial asthma and the like. The author's patient had chronic mucous colitis and chronic blepharoconjunctivitis. Intestinal intoxication was probably responsible for both, because the ocular symptoms improved or got worse simultaneously with the intestinal disorder. Vaccination with lactose-nonfermenting bacteria of the patient's intestinal flora cured the intestinal disorder and the blepharoconjunctivitis.

J.A.M.A. (W. ZENTMAYER).

RHEUMATIC INFLAMMATION OF EYE. O. MARCHESANI, Klin. Monatsbl. f. Augenh. **106:** 1 (Jan.) 1941.

The term rheumatic disease of the eye has not been defined. It has been accepted for inflammations of the sclera, episclera, iris, cornea, eye muscles and Tenon's capsule; it was not applied to inflammations of the choroid and ciliary body until a few years ago. Recent findings by the author and by other writers prompted him to consider rheumatism as the cause in many cases of uveitis and made him discard the idea of a focal or tuberculous origin in other cases. He observed rheumatic inflammation histologically in a number of eyeballs with chronic uveitis. Nodular formations represented typical forms of reaction in rheumatism as well as in tuberculosis (tuberculoid granuloma). Of 110 patients with uveitis Marchesani found active tuberculosis in 6, closed tuberculosis in 21, tonsillitis in 51, infection of the teeth in 66 and rheumatism in 38. The remaining patients suffered from such diseases as syphilis (1), sinusitis (4), otitis media (9), nephritis (4), parotitis (3) and heart and circulatory diseases (14). The presence of tonsillitis was established when pus or torpid fluid could be expressed; white plugs were not considered to be significant. In admitting the occurrence of rheumatic iritis without rheumatism, Marchesani refers to Pillat's finding of 60 per cent and 45 per cent of patients, respectively, with acute and with chronic rheumatism of the joints who had gone through a previous attack of choroiditis. The author observed choroiditis immediately after vaccination for typhoid and scarlatina, a process of pathergasia in his opinion. Most of the patients with nonspecific, autogenous uveitis experienced the onset between the twentieth and the thirtieth year or, in the case of women, during the menopause. The treatment consists in care of the nasopharynx, rest and administration of salicylates, aminopyrine and quinine. Gold therapy yielded good results antiallergically. K. L. STOLL.

Glaucoma

THE USE OF DORYL IN THE TREATMENT OF GLAUCOMA. S. T. CLARKE, Am. J. Ophth. **25:** 309 (March) 1942.

Clarke draws the following conclusions:

"1. Doryl [carbaminoylcholine chloride] is a parasympathomimetic agent capable of lowering the ocular tension in glaucoma.

"2. Doryl may be given in 0.75-percent concentration, which is much less irritating than other commonly used drops in the treatment of glaucoma.

"3. Doryl varies in effectiveness. Some patients maintain much lower tensions under doryl than under other drugs. Many patients are better controlled by doryl than by 2-percent pilocarpine. In a few patients doryl is not so effective as 2-percent pilocarpine. The action of doryl is usually about as strong as that of a mixture of 2-percent pilocarpine and 0.5-percent eserine [physostigmine].

"4. One of the most important considerations to be borne in mind when using doryl drops is that slight massage greatly increases the absorption and effectiveness of the drug.

"5. Doryl is valuable as a "rest therapy." Its use for a time seems to reduce a patient's tolerance to other miotic drugs so that they are more effective again after the period of doryl administration.

"6. Doryl is an effective substitute for other miotics which have caused a development of sensitivity in the patient accompanied by dermatitis and conjunctivitis. The use of doryl in such cases cures these annoying symptoms.

"7. Doryl is not presented as a substitute for all other pharmacologic agents used in the treatment of glaucoma. It does possess properties (non-irritating, effective lowering of tension in many patients) which make it a valuable drug to augment the armamentarium of conservative treatment of glaucoma."

W. S. REESE.

Hygiene, Sociology, Education and History

DISABILITY LAWSUIT FOLLOWING SUCCESSFUL BILATERAL CATARACT EXTRACTION. R. W. DANIELSON and J. C. LONG, Am. J. Ophth. **25:** 164 (Feb.) 1942.

An interesting lawsuit was decided against a patient who had both eyes successfully operated on for cataract and who sought compensation for "irrecoverable loss of sight in both eyes."

W. S. REESE.

Lens

PROCEDURES IN INTRACAPSULAR CATARACT EXTRACTION. D. B. KIRBY, Am. J. Ophth. **25:** 269 (March) 1942.

Kirby reviews the different methods of intracapsular cataract extraction and proposes a new method for cases in which the zonule proves resistant and unyielding to the ordinary safe and average pressure, traction and rotation. This consists of stripping the zonular membrane from the superior equator of the lens in direct view of the surgeon.

W. S. REESE.

Neurology

SYMPTOMATOLOGY OF OCCIPITAL ANGIOSPASMS: REPORT OF A CASE. J. TATÁR, Klin. Monatsbl. f. Augenh. 105: 543 (Nov.) 1940.

An oculist presented himself at the ophthalmic clinic fifteen minutes after slipping on an ice-covered sidewalk. The back of his head struck the ground, and, without losing consciousness, he observed reduction of his vision to counting of fingers. Fantom motions, resembling waves, were observed in the temporal fields, accompanied by metamorphopsia and macropsia. Full vision returned after fifteen minutes, but constructive alexia remained.

All symptoms disappeared forty minutes after the accident, and no objective changes remained. Associating these symptoms with those described by Benedek, Hüttl and Renz and with similar angiospastic disturbances of eclampsia, the author considers their origin to be cerebral angiospasm, that is, vasoconstriction in the area striata and the surrounding regions.

K. L. STOLL.

Retina and Optic Nerve

UNILATERAL INVOLVEMENT OF THE OPTIC NERVE IN HEAD INJURIES. F. C. RODGERS, Brit. J. Ophth. **27:** 23 (Jan.) 1943.

Rodgers reports a series of cases of head injuries with unilateral involvement of the optic nerve. He summarizes as follows:

"1. Twenty cases of unilateral atrophy due to head injury, none of which was fatal, were investigated.

"2. The clinical picture is that of a primary atrophy, but why the disc changes its color, and the arteries their form, is not clearly understood.

"3. Current literature, with theories based on post-mortem findings, is not completely relevant. Our results have been obtained as a result of clinical and X-ray investigations only.

"4. Stereoscopic photographs in nine out of thirteen cases revealed a distorted foramen on the side of the defective eye. This distortion was reported at its least definite to be 'almost certainly traumatic.' "

"5. There is a school of thought which considers that this frequent occurrence of traumatism of the canal has a mechanical basis, that the canal is, in fact, 'locus minoris resistentiae.' It is thought, however, that there will be no traumatism of the canal where the blow is delivered in the same direction as its long axis.

"6. Clinical investigation suggests that in addition to the bony lesion, associated haemorrhage from nutrient or septal vessels, or both, plays a large part in many of the cases.

"7. Haemorrhage alone may result, and such cases would of course have a slightly better prognosis.

"8. As the defect cannot be recognised with certainty at an early stage, and as the possibility of parenchymatous bleeding cannot be excluded, effective treatment appears to be impossible."

Brief clinical histories of the cases observed are included, the results are given in tabular form and the several theories that have been advanced to explain the nerve involvement are stated.

The article is illustrated.

W. ZENTMAYER.

TECHNIC OF RETINAL OPERATIONS. A. VOGT, Klin. Monatsbl. f. Augenh. 105: 269 (Sept.) 1940.

Despite the help of a number of apparatus, the localization of a rupture in the retina is rendered difficult in many cases. Cloudiness of the media, hemorrhages in the vitreous and exudations may obstruct the view; the foam of retinal coagulation may be hidden by hyperplasia of the retina. Vogt describes a new method of localizing a retinal tear at the ora serrata by markings on the sclera. He examined 10 fairly normal eyeballs, which he bisected at the equator after marking the insertions of the rectus muscles. He found that needles 0.18 mm. thick (the size of those used in katholysis) if radially inserted at the edge of the ora serrata appeared at the insertions of the rectus muscles. In an attempt, therefore, to strike a retinal tear at the ora serrata, the insertion of the closest rectus muscle is exposed, and then punctures are made or katholysis performed at the edge of the tear close to the ora serrata. Afterward the area at the other edge of the tear is repeatedly punctured. The two extremities of the tear are treated in the same manner. Errors may occur due to variation of the length of the eyeball (myopic or hyperopic) and to obliquity of the insertion of the rectus muscle. The margin of the ora, furthermore, is not a straight line, but is ragged, with prominences especially noticeable at the nasal side. The technic is the same if the tear is somewhat distant from the ora, except for the necessity of reaching the retinal edge of the tear farthest from the ora. The insertions of the rectus muscles show a dorsoventral elongation in some cases. When this condition is present errors may be avoided by making a broader zone of punctures. Errors in the myopic eye growing out of the length of the eyeball are less important, because the posterior and not the anterior segment is stretched. E. Fuchs and M. Salzmann found the insertions of the rectus muscles approximately at the same distance from the limbus as in normal eyes. Also, only the posterior portion of the sclera undergoes distention in axial myopia. In the hydrophthalmic eye, on the other hand, the entire sclera is ectatic. Vogt stresses the thickness of the sclera of the posterior segment as a source of errors. He cautions that in the eye with high axial myopia the sclera is so thin in the area of the macula lutea that katholysis with a diathermic needle 0.5 mm. long will perforate not only the sclera but the retina. Therefore, a needle 0.25 mm. long will suffice in cases of a tear in the macula. In repeated operations on the eye with axial myopia there may be danger of perforation in separating adhesions with knife or scissors. The paper is illustrated with eight photographs.

K. L. STOLL.

Trachoma

STUDIES ON THE INFECTIVITY OF TRACHOMA. L. A. JULIANELLE and J. E. SMITH, Am. J. Ophth. **25: 317** (March) 1942.

Julianelle and Smith give the following summary:

"Trachomatous tissues capable of inducing specific infection in monkeys were subjected *in vitro* to the action of sulfanilamide. The time of exposure to the drug was from four-and-one-half to five hours at room temperature and the final con-

centrations of sulfanilamide tested were 1:300, 1:3,000 and 1:30,000. The experiments were controlled by exposing the same tissues in similar fashion to an equivalent volume of physiologic saline. After contact with the different solutions, the tissues were tested for infectivity. Under these conditions, it was not possible to demonstrate that sulfanilamide has any appreciable effect on the infective capacity of the virus of trachoma."

W. S. REESE.

Tumors

INTRAEPITHELIAL EPITHELIOMA OF THE CORNEA AND CONJUNCTIVA (BOWEN'S DISEASE). J. S. MCGAVIC, Am. J. Ophth. **25:** 167 (Feb.) 1942.

McGavic discusses Bowen's disease as a lesion of the skin and also of the mucous membrane. He reports 5 cases in which the cornea was affected and gives the following summary:

"1. Bowen's disease is an intraepithelial epithelioma which shows lateral spread *in situ* and is very slow to invade or metastasize. The histopathologic picture varies from ordinary epithelioma *in situ* to Bowenoid epithelioma.

"2. The diagnosis depends upon microscopic examination, but may be suspected clinically.

"3. Complete surgical excision is the treatment of choice. Inadequate treatment by radiation, cautery, or chemical application is to be avoided.

"4. Ocular involvement by Bowen's disease is here reported for the first time."

W. S. REESE.

Uvea

OCULAR INFLAMMATIONS OF FOCAL ORIGIN. D. ANASTASSOFF, Ophthalmologica **104:** 136 (Sept.) 1942.

Anastassoff reports 6 cases of iridocyclitis, of which the origin was in an infected dental root in 4, the tonsils in 1 and the prostate in 1. In 2 cases of episcleritis a focus of infection existed in the tonsils. By means of Rosenow's technic Anastassoff was able to produce an iridocyclitis in rabbits and an immature cataract. Bacteriologic examination disclosed no specific agent, this fact leading the author to conclude that the lesions were of a toxic nature.

J. A. M. A. (W. ZENTMAYER).

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

ALFRED COWAN, M.D., *Chairman*

WARREN S. REESE, M.D., *Secretary*

February 18, 1943

Malignant Exophthalmos: Three Cases. DR. A. S. CRANDALL.

In case 1, exophthalmos developed in a 48 year old white man one month after thyroidectomy for exophthalmic goiter. Proptosis increased to such an extent that exposure keratitis was imminent and the visual acuity dropped to 20/400 in each eye. A Naffziger operation was done on one side and a Shugrue operation on the other, without benefit. The patient was given desiccated thyroid and diethylstilbestrol without benefit. He improved decidedly after irradiation of the pituitary.

In case 2, progressive exophthalmos developed in a 33 year old white man seven months after thyroidectomy for diffuse toxic goiter. After administration of desiccated thyroid and diethylstilbestrol and irradiation of the pituitary exophthalmos remained stationary, conjunctival edema cleared and vision improved.

In case 3, rapidly increasing exophthalmos and a decrease in vision developed in a 45 year old Negro woman with exophthalmic goiter. After administration of potassium iodide and diethylstilbestrol and irradiation of the pituitary, the exophthalmos remained stationary and the vision improved.

Malignant exophthalmos has been shown to be due to edema of the orbital tissues. The edema is caused by a hormone from the anterior lobe of the pituitary gland. Sex is another factor. Good results have been reported from roentgen irradiation of the pituitary gland and orbits combined with administration of desiccated thyroid and estrogenic substances.

DISCUSSION

DR. E. ROSE: The term "malignant exophthalmos" implies the possibility that some malignant process is responsible for the exophthalmos, whereas this is usually not the case. "Progressive exophthalmos" might be a better term.

Ginsberg in 1939 cited forty-five writers who had advanced theories—some of these duplicating others—in an effort to explain exophthalmos. Some of the causes put forth are extremely bizarre: an excessive amount of vitreous, excessive deposits of retrobulbar fat, extreme congestion of the vessels of the orbit and variations in size of the sphenoid fissure.

One of the theories most prominent, apparently, for a number of years involved hypertonus of the muscle of Müller. This received support from the fact that in certain experimental animals it was possible with considerable regularity to produce exophthalmos by stimulation of the cervical sympathetic nerves, and it was shown a number of years ago by McCallum and Dandy at Johns Hopkins that in dogs whose müllerian muscles were transversely cut, such stimulation no longer produced protrusion of the eyeball.

However, the fibers in Müller's muscle in man are not nearly so well developed as they are in some of the lower animals, such as the dog, and a study by Friedgood, Cattell and Beetham, in Boston, gave considerable support to the idea that the cervical sympathetic nerves had nothing to do with exophthalmos. In 10 patients who were having thyroidectomies for hyperthyroidism, they stimulated the cervical portion of the sympathetic trunk while the neck was open.

In the only patient who had well defined exophthalmos associated with the hyperthyroid state they were able to demonstrate protrusion of the eyeball (1 to 2 mm.). In the others, who had hyperthyroidism without exophthalmos, they were unable to produce any demonstrable increase in the prominence of the eyes.

Not all patients lose their exophthalmos after subtotal thyroidectomy. Soley, in San Francisco, and Galli-Mainini, at the Massachusetts General Hospital, in Boston, in measuring the exophthalmos of a group of patients before and after thyroidectomy, found that few actually showed a regression; the exophthalmos either remained the same or got worse. The deceiving factor seems to be the loss of the increased tone of the muscles of the upped lid, which often causes disappearance of the retraction of the upper lid after thyroidectomy and thus gives the false impression that the exophthalmos has receded, whereas careful measurements do not bear out this impression.

In this type of exophthalmos, the offending organ seems to be the pituitary rather than the thyroid, and probably the anterior part of the pituitary, in some way not yet fully understood, produces a secretion or other factor which has the ophthalmotropic effect which Dr. Crandall mentioned. This produces the changes in the retrobulbar tissues of the orbit which, combined with the relaxed tension of the extraocular muscles, result in forward propulsion of the eyeball.

This process can stop spontaneously at any point. Friedgood, who has written one of the best reviews of the entire subject, stated the belief that the exophthalmic process can be divided into a reversible and an irreversible stage. The reversible stage is that in which the protrusion of the eyeball is the result of edema of the retrobulbar structure. If this edema subsides, the eyeball recedes into the orbit; this explains the fact that many patients with exophthalmos who die lose their exophthalmos soon after death; the edema disappears. In life, after a certain length of time it is replaced by round cell infiltration, which produces a brawny induration of the structures; then the exophthalmos has reached the irreversible stage.

One must be cautious in interpreting the results of therapy. So few patients have been treated by the means outlined by Dr. Crandall that there are insufficient data from which to draw any valid conclusion. Medical treatment is still based largely on theory. One irradiates the pituitary on the assumption that it is responsible. It is not known how effective that irradiation is. Next, one sometimes gives desiccated thyroid with the thought that it will have some inhibitory effect on the anterior lobe of the pituitary. This again is theoretic endocrine medicine, which may not have sufficient basis in fact. One also gives estrogenic substances, either natural or synthetic (diethylstilbestrol), because there is experimental evidence to suggest that they have an inhibitory effect on the anterior lobe of the pituitary. Again one is working on a basis of theory. So I think that care must be taken in interpretation of results of treatment directed to the pituitary, especially since it is known that exophthalmos can stop at almost any given point.

Speaking as an internist interested in endocrine medicine, I agree with Dr. Crandall that one should approach with extreme caution operative treatment of thyrotoxic patients in whom the exophthalmic syndrome dominates the thyrotoxic picture. In the face of severe or rapidly progressive exophthalmos, especially if it is associated with edema of the lids, chemosis and congestion of the conjunctiva, and particularly if the thyrotoxicosis is not severe, surgical intervention calls for great caution. If the patient responds in an exaggerated fashion to the administration of iodine, one should hesitate to operate. It has been pointed out that instead of showing a gradual drift to normal in the basal rate (in ten to fourteen days) some patients with mild thyrotoxicosis associated with severe exophthalmos show a quick drop in the basal rate to a substandard level.

In cases such as the third one reported by Dr. Crandall, one can depend on iodides or a combination of iodide therapy with roentgen ray treatment to the anterior lobe of the pituitary and to the thyroid.

A practical lesson in general medicine has been learned from such cases, and future developments in this field are awaited with interest.

DR. F. H. ADLER: Dr. Crandall and Dr. Rose have shown that in progressive exophthalmos the proptosis at the beginning of the disease is out of all proportion to the thyrotoxic symptoms. It is extremely difficult to judge the degree of exophthalmos, since normal readings, varying so much from one patient to another, depend on the physiognomy. Some persons have more prominent eyeballs than others, and the only means of determining in an individual case whether the degree of protrusion is abnormal is a difference in the measurements of the two sides or a change in the measurements over a period of time. It has been my experience that patients with this condition show little evidence of thyrotoxicosis, judged by tachycardia, sweating, tremor and loss of weight.

DR. W. E. FRY: In the first case Dr. Crandall reported, a Naffziger operation was done on one side and a Shugrue on the other. It had not been the intention to obtain a comparison of the effects of the two operations. The Naffziger was done first, and because of technical difficulties it was not possible to complete the operation on the other side. Therefore, another type of operation was decided on, and the Shugrue was done.

Approximately the same amount of decrease in exophthalmos was obtained with each operation, about 2 mm. As can be seen from the figures, the amount of decrease obtained with roentgen ray and medical treatment was much greater.

Vogt-Koyanagi Syndrome. DR. H. ABRAMS.

Impressed by the excellent report of Carasquillo in the ARCHIVES for September 1942 (page 385), I wish to present 2 patients with features of the Vogt-Koyanagi syndrome.

The first, a Negro schoolboy aged 16, was seen at the Wills Hospital Jan. 6, 1943 complaining of pain in the left eye and poor vision. There was no family history of ocular disease or pigmentary changes of the skin or hair. During childhood the patient had had measles, chickenpox and mumps, with no complications. In January 1941 a patch of vitiligo was noted on the right cheek, and it gradually spread over the face to involve the right side of the nose and inner canthus region. When it reached the lid margins, poliosis was noted. The patient denied any hearing difficulties or tinnitus.

The patient was thin but in good general health. Physical examination revealed an area of vitiligo on the right side of the face, involving a portion of the cheek, the side of the nose and the inner canthus region. The inner third of the upper and lower lids had patches of vitiligo and contained pure white cilia. The visual acuity on admission was 6/5 in the right eye and 6/60 in the left (Snellen). There were moderate circumcorneal injection, numerous deposits on Descemet's membrane, many floating opacities of the vitreous and marked retinal edema, especially surrounding the disk. The macular area could not be clearly demarcated. One month later the visual acuity was unchanged. Examination with the biomicroscope revealed many old pigment granules on the posterior surface of the cornea, with some endothelial disturbance between the granules. No cells were noted in the deep anterior chamber. There were some areas of pigment on the anterior capsule of the lens along the pupillary border. Urinalysis, chemical examination of the blood, a Wassermann test of the blood and a Mantoux test gave negative results.

The second patient, a white laborer aged 21, complained of failing vision and pain in the right eye. Three weeks after the onset of pain the eye became red and irritable; photophobia and lacrimation were constant. One week later the cilia of the right upper lid (inner half) turned white, and subsequently they fell out. Tinnitus was present for a short time.

The patient was a well nourished but "nervous" type. The visual acuity when he was first seen was 6/12 in the right eye with and without glasses and 6/12 in the left eye without and 6/9 with glasses. There were a patch of vitiligo on the right upper lid at the margin and finely pointed white cilia at the margin of the inner half of the lid. Ocular examination revealed a phlyctenular-like

keratoconjunctivitis, accompanied by anterior uveitis; it was corroborated by examination with the biomicroscope. When the uveitis had quieted and most of the white lashes had fallen out, the visual acuity in the right eye was 6/12 without glasses and 6/9 + 3 with glasses and in the left eye was 6/12 without glasses and 6/9 with glasses. The only residual manifestations in addition to the white cilia and area of vitiligo were opacities of the vitreous and fine pigmentary deposits on the anterior lens capsule.

I believe that since these patients manifested the symptoms (i. e., uveitis with poliosis, vitiligo, alopecia and dysacousia) reported by Carasquillo, although to a milder degree and unilaterally, they should be classified as having the Vogt-Koyanagi syndrome.

DR. ALFRED COWAN: This syndrome was first described by Vogt. Later, a number of cases that had already been reported were collected and with about 6 cases of his own were reported by Koyanagi. Now it seems awkward to have to say uveitis with vitiligo, deafness and alopecia. So, since Vogt was the first to describe the syndrome, there may be some justification in naming it "Vogt's syndrome"; but I should like to ask Dr. Abrams why he added the name of Koyanagi.

Papilledema in Acute Disseminated Lupus Erythematosis. DR. W. H. STEELE.

A brief outline of the pathologic picture of acute disseminated lupus erythematosis was given and an outline of the fundus lesions found in association with this disease presented. The following case was reported:

The patient, a white woman aged 20, was admitted Jan. 3, 1943. Two months previously, after a cold, she had been admitted to another hospital with a diagnosis of facial erysipelas. A course of therapy with sulfonamide compounds was started, and after a few weeks the patient was discharged. Immediately after discharge there developed a succession of fleeting pains in the joints, malaise and dyspnea. The temperature on admission was 104 F. and the blood pressure 100 systolic and 60 diastolic. Physical examination showed a red-brown indurated cutaneous lesion in the "butterfly area" of the face, signs of consolidation at the base of each lung and enlargement of the heart with friction rub. There gradually developed pericardial, pleural and peritoneal effusions, with hepatomegaly, respiratory embarrassment and periods of semiconsciousness. Neurologic examination gave negative results. A lumbar puncture on two occasions showed increased pressure of the cerebrospinal fluid.

Ophthalmologic examination showed mild conjunctival injection. Examination of the right fundus showed blurring of the disk margins, hyperemia of the disks with elevation of 4 D. and moderate peripapillary edema obscuring vessels and containing many large, white, fluffy exudates with flame-shaped hemorrhages and dilated veins. The left fundus was similar. Frequent examination failed to show any change in the fundus picture. The patient died ten days after admission.

DR. W. E. FRY: During the last few years I have been interested in observing the variety of conditions that have papilledema as an important feature, and I think this is one that can be added to the list. The papilledema was definite. It measured 4 to 5 D., and associated with it was an increased pressure of the spinal fluid. That, to me, was the interesting feature of the case, although there were others that would be interesting from another point of view.

Malignant Melanoma of the Choroid. DR. G. M. JOHNSON.

A 42 year old white truck driver entered the Wills Hospital clinic on June 20, 1942 complaining of pain and redness of the left eye. He gave a vague history of having pain in the eye one year before but no history of haloes. A week before he had had pain in the eye which kept him awake at night; he had some teeth removed on June 15 and said that the eye became worse.

The family history was noncontributory. Examination showed the right anterior chamber to be moderately shallow but otherwise normal. In the left eye the conjunctiva was chemotic and red. The left cornea was slightly hazy, the anterior chamber obliterated and the iris atrophic and bulging forward. The pupil measured 4 mm., was fixed and had a greenish reflex, and the lens was hazy. The vitreous was obscured. There was severe photophobia.

The vision was 6/6 in the right eye corrected and perception of hand movements at 12 inches (30 cm.) in the left. There was good light projection. The tension was 17 in the right eye and 66 in the left.

The diagnosis was acute congestive glaucoma.

June 22 an Elliot trephine operation was done; June 23 the conjunctiva was chemotic and red, and the eyeball felt very hard on palpation; June 24 there was less chemosis, the anterior chamber was shallow and the eyeball felt hard as a rock on palpation; June 27 a Frost-Lang enucleation was performed. Recovery was uneventful.

The pathologic diagnosis was malignant melanoma of the choroid, spindle cell type B, glaucoma stage; choroidal, subchoroidal and subretinal hemorrhage, and detachment of the choroid and retina.

This case is presented because it is so typical. The sudden onset of unilateral hypertension unrelieved by operation for glaucoma, with atypical fields, suggests neoplasm.

DISCUSSION

DR. E. B. SPAETH: Apparently I have difficulty in learning some things, because this is the third patient admitted with acute inflammatory glaucoma whose underlying malignant process was undiagnosed.

The first of the 3 had acute unilateral congestive glaucoma and had an iridectomy performed shortly after admission. The following day the tension was no lower. For some unknown reason I presumed that the condition was hemorrhoid glaucoma. An enucleation was done and an undiagnosed malignant process was found.

The second patient was a man considerably older than the first. He was admitted with acute congestive glaucoma and was treated conservatively for one or two days. An iridectomy was done with general anesthesia. The cornea cleared at the time of the operation, but the tension did not recede. It was remarkable to place a spatula on the eye and find it as hard as it had been before the anterior chamber was opened. The patient had the barest of light reflexes in the superior nasal portion of the fundus. I thought that he had a huge subchoroidal hemorrhage. The next morning the eye was enucleated, and an undiagnosed malignant melanoma was discovered.

The third patient's condition was almost classic but there was a bit more congestion than was shown by the first 2 patients. It could be considered subacute congestive glaucoma. The diagnosis of malignant melanoma was not made until after enucleation, the enucleation being done because the glaucoma did not respond to surgical intervention.

The cases of these 3 patients emphasize one thing: that unilateral glaucoma of high degree in the absence of a pertinent history, and regardless of the fields of vision, may well be caused by an unsuspected intraocular malignant melanoma.

DR. M. BLAIR: I should like to say that I have had an experience similar to that of Dr. Spaeth; I have observed 5 cases in which malignant hypertension caused me to do first an iridectomy for the relief of pain and ultimately an enucleation because the iridectomy made matters infinitely worse and biopsy revealed melanosarcoma of the choroid. In 1 case metastatic sarcoma of the liver developed and the patient lived less than five months after enucleation.

The difficulty is that one sees the patient too late. An early diagnosis would mean earlier enucleation, with less danger of metastasis, and less embarrassment for the surgeon, who could determine the nature of the lesion by transillumination.

Glass Blowers' Cataract. DR. G. J. DUBLIN.

Glass blowers' cataract is a rare condition, particularly at the present time, when glass manufacturing is done almost exclusively by machinery. The condition may occur in places where excessive heat is used in processing metals, being noted in sheet mill men, tin plate workers, blacksmiths and others. The cause has been claimed to be physical, that is, heat or excessive sweating, which precipitates some of the substances of the aqueous, or infra-red and ultraviolet light. A textbook description of this entity was presented, including mention of the period of onset and the frequent association with senile cataract in its later stages, which often masks the early symptoms.

A differential diagnosis of glass blowers' cataract from senile saucer-shaped, complicated and traumatic contusion cataract was given. A detailed description of the case of a glass blower 82 years old with bilateral involvement was offered. Particular attention was called to the fact that the most pathognomonic change in this condition is lamellar separation. Three types of this separation were noted, and a description of each, with the various diseases with which it is associated, was given.

DISCUSSION

DR. A. COWAN: I should like to say that Dr. Dublin's case was the first I ever heard of in which the patient was a glass blower. I saw a puddler, a laborer and a carpenter affected. I agree with Dr. Dublin; I cannot see how any one could diagnose the onset of glass blowers' cataract by signs similar to those of the ordinary types of cataract. It seems obvious to me that the anterior zonular lamella does cover the entire anterior surface of the lens. In capsular cataract erosion evidently starts behind the iris, and usually the central portion remains intact, while in glass blowers' cataract the separated zonular lamella remains a homogeneous, transparent, more or less intact membrane.

I have never seen a place that would indicate a break, and it always seems that if the separated membrane were extended it would go down below the lower border of the pupil. The break must take place near the equator of the lens. In the one instance the anterior zonular lamella is eroded, while in the other there is separation of a more or less intact zonular lamella. It is probable that heat, while it may be a factor, is not the whole cause of this condition.

DR. M. BLAIR: Something constructive might be done by using Shahan's electrothermophore experimentally on the cornea of animals and recording the traumatic effects of heat of various intensities with various lengths of exposure, or, even better, by duplicating the actual conditions of workers before white heat. These men, even though presumably protected by cobalt glasses, form a large percentage of those afflicted with cataract, and I can hardly be convinced that glass blowers could escape the results of similar exposure, especially if it was continued over many years.

DR. I. TASSMAN: The question arises as to how much indirect traumatism enters into the production of cataracts. Dr. Dublin implied that the type of cataract reported on may occur in persons other than glass blowers, for example, in furnace workers. Would not indirect traumatism play some part in the production of this particular type of cataract? I do not know how much blowing glass blowers must do today, but in years past they probably did a great deal, which might have caused considerable increase in the pressure and distention within the eyeball, leading to indirect traumatism to the lens. I do not believe the question of heat in its relation to the production of cataract has ever been definitely settled. Some years ago it was shown by actual experiment that the temperature in the neighborhood of the crystalline lens was not increased as the result of exposure of the eyes to extremes of heat, most of which is absorbed by the iris, which acts as a screen. There must be another important factor in the production of such cataract.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY, AND NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

Joint Meeting, March 15, 1943

DR. DANIEL B. KIRBY, *Chairman, New York Academy of Medicine, Section of Ophthalmology*

DR. ISADORE GIVNER, *Chairman, New York Society for Clinical Ophthalmology*

DR. R. TOWNLEY PATON, *Secretary, New York Academy of Medicine, Section of Ophthalmology*

DR. BENJAMIN ESTERMAN, *Secretary, New York Society for Clinical Ophthalmology*

SYMPOSIUM: ROUND TABLE DISCUSSION OF NONSURGICAL THERAPY IN OPHTHALMOLOGY

Vasodilators and Their Action on the Central Retinal Artery

QUESTION: Dr. Adler, is there any evidence that vasodilators act on the central retinal artery or its branches?

DR. FRANCIS HEED ADLER, Philadelphia: There is fairly good evidence that vasoconstrictor fibers in sympathetic nerves supply both the uveal and the retinal system of vessels in the interior of the eye. There is indirect experimental evidence that the uveal blood vessels can be dilated by vasodilator drugs, but there is no direct experimental evidence that the central retinal artery or its branches may be so affected. I think this is what one might expect. In the first place, the vessels inside the eye are like those inside the brain and have no need of a very active control of their caliber. Further, the retinal system is so small, as compared with the uveal system, that it would be difficult to get any direct evidence of a change in caliber in it. Practically no experimenters have been able to show any change in the caliber of the central retinal artery or its branches with vasodilator drugs. I do not see how any one could hope for such enormous dilatation that the change would be measurable in a single arteriole.

If one administers amyl nitrite to an experimental animal and measures the intraocular pressure and the blood pressure simultaneously, there is nearly always a fall in both pressures, for as the general blood pressure falls, the intraocular vessels are more or less emptied of blood, and accordingly the pressure inside the eyeball falls. I have seen on several occasions, however, just before the fall in general blood pressure took place, a slight rise in intraocular pressure, which was undoubtedly due to a vasodilator effect of the amyl nitrite on the intraocular circulation. I think this is definite proof that nitrites do dilate the intraocular blood vessels.

One is probably justified in administering nitrites in the treatment of any condition of the eye which may be due to arterial spasm, but I do not believe that vasodilator drugs are indicated for all ocular diseases. In a recent article such drugs were recommended not only for tobacco amblyopia, which the author claimed is due to a constriction of peripheral vessels, but for a condition called choroidosis centralis serosa, which the same author claimed is due to an increased permeability of the choriocapillaris.

Uveitis with Secondary Glaucoma

QUESTION: Dr. Gifford, how do you handle uveitis with secondary glaucoma?

DR. SANFORD R. GIFFORD, Chicago: If the tension is elevated only slightly (not over 32.5 Schiøtz) and only occasionally, I treat the uveitis in the usual manner, giving atropine sulfate if active iridocyclitis is present. I use salicylates or sulfonamide compounds and look for the cause. If a definite focus is disclosed, I do not hesitate to advise removal or treatment. If the condition is syphilitic, I believe in energetic treatment, and if it is gonococcic, I use sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole).

If the tension remains above 32.5, I try paracentesis, repeated in three days if necessary, and usually continue the use of atropine. Some patients are helped by intravenous injection of sorbitol, but not all. I have not tried retrobulbar injection of alcohol.

If the uveitis is chiefly posterior, or is becoming quiet, I stop giving atropine and try a mild miotic, for example a 1 per cent pilocarpine nitrate solution, for a few days, stopping if the tension comes down, and using 10 per cent neosynephrin hydrochloride solution at intervals to dilate the pupil. I am afraid of epinephrine, as I have seen it provoke acute attacks of glaucoma, and hesitate to use much neosynephrin, although I have not seen an acute attack provoked by it.

If the pupil is already secluded, I continue the use of atropine and do Fuchs's double iris puncture instead of paracentesis.

If the tension is above 35 and returns to this level promptly after paracentesis, I do iridectomy, but I have rarely been forced to do this in a case of active iridocyclitis. In preparation, I administer 100 cc. of 50 per cent sorbitol solution or dextrose by vein six hours before operation and carry out retrobulbar injection of procaine hydrochloride and epinephrine of 4 per cent procaine hydrochloride solution, followed by use of atropine sulfate if the iritis is active.

In any case I watch the tension long after the uveitis has subsided and operate in a quiet period if it persists.

QUESTION: Dr. Schoenberg, have you any questions on secondary glaucoma?

DR. MARK J. SCHOENBERG: I wish to object to the term secondary glaucoma; I do not think there is such a thing. There is only one form, and that is primary glaucoma. So-called secondary glaucoma is not glaucoma at all. It may be iridocyclitis, subluxation of the lens, thrombosis of the central retinal vein, tumor, etc., each one of which causes ocular hypertension but none of which causes glaucoma. I would suggest using the term secondary ocular hypertension instead of secondary glaucoma.

DR. SANFORD R. GIFFORD, Chicago: Paracentesis has only a temporary effect in some cases but will adways reduce the tension for a few hours at least and give the patient respite; therefore I repeat it. After a second or third paracentesis, if the uveitis is subsiding the tension may remain under control. Sometimes all these measures are unavailing, and one must do something else.

Treatment of Simple Glaucoma

QUESTION: Dr. Schoenberg, what is your routine treatment of simple glaucoma? And what are the indications for the use of physostigmine and pilocarpine?

DR. MARK J. SCHOENBERG: The short time at my disposal does not permit me to give a complete answer. I shall enumerate only the essential points. There are a number of guiding principles: first, to promote the general health; second, to eliminate or alleviate disease whenever possible, and third, to decide the treatment according to (*a*) the stage of glaucoma, (*b*) the type of glaucoma, (*c*) the age of the patient and (*d*) the type of patient.

As to the drugs employed for local treatment, one must make up one's mind whether the physostigmine-prostigmine, or the acetylcholine-mecholyl-doryl group or pilocarpine (alone or in combination) is suitable for the patient. (Doryl is carbaminoylcholine chloride.)

Establishing the indications for a certain drug depends on the intimate understanding of a certain number of facts revealed by the theory of chemical mediations of nerve impulses.

The next step after establishing the indications is to work out the frequency, the dose and the timing of the instillations.

QUESTION: Should tobacco and alcohol be interdicted for patients with glaucoma?

DR. MARK J. SCHOENBERG: Prohibition of the use of alcoholic beverages depends on the general condition and age of the patient. In old age, the need of a stimulant and of vasodilation is greater, and alcohol when used with moderation is beneficial. Young people if permitted to indulge in alcoholic beverages are prone to use them to excess.

Tobacco is responsible in many people for chronic nasopharyngeal irritations, lack of appetite, vitamin deficiencies, vascular spasm, toxic amblyopia, etc. It should be forbidden patients with glaucoma.

Ocular Tuberculosis

QUESTION: Dr. Woods, in what expressions of ocular tuberculosis is tuberculin of value, and what is your routine treatment?

DR. ALAN C. WOODS, Baltimore: I believe the value of tuberculin in ophthalmology lies in its desensitizing effect on the ocular tissues. In line with this view, tuberculin would, naturally, be of greatest value in cases in which the ocular sensitivity was high and in which the patient was susceptible to tuberculin therapy. These are the criteria which I believe influence the successful use of tuberculin, rather than any especial manifestation of the disease. The first point is difficult to determine because there is no safe clinical test for ocular sensitivity. Judging by experimental studies, if the cutaneous sensitivity is high, one is safe in assuming that the ocular sensitivity is also high. This is the situation in about two thirds of the cases of ocular tuberculosis. But if the cutaneous sensitivity is low, the ocular sensitivity may still be high, for it is known from experiments that a tuberculous disease in the eye may often not affect the cutaneous reactivity to tuberculin, although the eyes are extremely sensitive. Acute inflammation usually signifies high local sensitivity. One must, therefore, base one's judgment of the ocular sensitivity on the cutaneous reactions and the clinical picture in the eye. The second point which underlies successful tuberculin therapy is the ability of the patient to take treatment. Unfortunately, there are patients so exquisitely sensitive that they cannot take even the most minute doses of tuberculin without systemic, local and even focal reactions. One finds by a trial and error system that tuberculin is of no value, is even harmful, in the treatment of such patients. I should say, therefore, that tuberculin is of value in ocular tuberculosis when there is high ocular sensitivity and the patient can take tuberculin without undue reactions. Tuberculin is of greatest value in the treatment of patients who have sufficient resistance or immunity to handle the infection when the sensitivity factor, which is responsible for the inflammatory and destructive phases of the lesion, is removed by desensitization.

As to routine treatment, I believe the cardinal point is to keep the dose below the patient's individual point of reactivity, increasing it as this point recedes. In practice, I use Denys' bouillon filtrate, usually starting with 0.00001 mg. and, provided there are no untoward reactions, increasing each dose by 0.00001 or 0.00002 mg. until 0.0001 mg. is reached. This dose is similarly increased until 0.001 mg. is given, and so on to higher doses. Injections are given in the early stages twice a week and in the later stages once a week. When a dose of 90 mg. is reached, it is given weekly for a minimum period of two years, to maintain the desensitization achieved. Otherwise sensitization recurs, with the danger of ocular relapses.

DR. I. RAPPAPORT: There is little I can say from the internist's point of view on the treatment of tuberculosis that will have any bearing on what Dr. Woods

said. I think, as do most ophthalmologists, that tuberculin therapy is of considerable value in the treatment of ocular tuberculosis, but most internists will agree that it is of practically no value in the treatment of tuberculosis in general. I should like to add that the initiator of so-called desensitization therapy in this country, Dr. Arnold Rich, from his more recent work has concluded that desensitization is not a factor, or at least, not the factor, in resistance, as he had assumed in his first work, in the early 1930's. He now is willing to admit that desensitization will help immunity in some instances, will not influence the resistance at all in other instances and will lower resistance in some instances. From the internist's standpoint, I would say that desensitization is just as little, or just as much, of value in aiding general resistance in tuberculosis as is so-called sensitizing therapy, which is still used by some workers, particularly abroad. Tuberculin therapy has practically no status from the internist's standpoint, and is no longer used, except by a few individual workers. It is never used in institutional therapy. From the clinical as well as the experimental standpoint, internists agree that tuberculin therapy is out of date.

QUESTION: How would you establish the diagnosis before you begin tuberculin therapy, Dr. Woods? How do you interpret the reactions in tuberculin therapy, and are the injections all given subcutaneously or intracutaneously?

DR. ALAN C. WOODS, Baltimore: May I first answer the question Dr. Rappaport brought up? Desensitization has practically no effect in increasing the resistance or immunity of the patient. I am well aware of the disrepute of tuberculin, which dates from the time of Virchow, and of the fact that tuberculin therapy has fallen from favor with internists. I think the reasons are obvious. In systemic tuberculosis the patient is excreting more tuberculin than he can handle, and, secondly, tuberculin therapy as often administered was pretty ghastly. The world might have been much better off if it had not been discovered. I am well aware of Dr. Rich's views and am sure Dr. Rappaport is in error in stating that Dr. Rich has modified them in the manner described. While, unfortunately, there is no method of stimulating the immunity of the patient, which in the last analysis accounts for the encapsulation of the lesion, if one does remove the sensitivity factor, I think one removes the factor responsible for the destructive stages in the tuberculous lesion.

In reply to the other questions, the diagnosis must be established, first, by the clinical picture of the eye, this being correlated with the results of histologic study of such pathologic material as is available. The clinical picture of ocular tuberculosis in animals is amazingly similar to that in human beings. A certain chronic type of lesion in some instances, a nodular type in others (which must be differentiated from sarcoid) and a widespread type of choroiditis (such as one sees in children) in still others suggest the tuberculous origin. In most cases of ocular tuberculosis the clinical picture first makes one suspect a tuberculous origin. The next step is to exclude the other possible causes: syphilis, brucellosis, sarcoid tumor (which is the most difficult to exclude) and possibly focal infection. Third, one can get some information from the cutaneous reactivity of the patient to tuberculin. If this is strongly positive it is circumstantial or corroborative evidence that one may be dealing with tuberculosis, but if it is negative it is of little help. I think it is chiefly on these factors, and on the evidence of a tuberculous reservoir elsewhere in the body, such as the hilar glands, that one must base the diagnosis. After all, it must be admitted that in many cases the diagnosis is only presumptive.

In reply to the other question, one should not start with a large dose of tuberculin. One can start with 0.00001 mg. I have rarely seen this dose cause an untoward reaction. The patient should be watched carefully and the dose raised only when the point of reactivity recedes.

In reply to the third question, I give tuberculin subcutaneously, but I am not sure that this is the right method. In animals, the intracutaneous method has possibly given better results. I hope to have some experimental evidence on this subject within another year. At present it is best to stick to the true and tried method and give tuberculin subcutaneously.

DR. FRANCIS HEED ADLER, Philadelphia: I should like to ask Dr. Woods whether patients with a high degree of cutaneous sensitivity who were treated successfully showed any diminution in cutaneous sensitivity.

DR. ALAN C. WOODS, Baltimore: In general, yes, but many did not. There is a good deal of evidence that tuberculin may filter out at an inflamed focus, and there may be such a thing as local desensitization of the eye.

Autogenous Vaccine Therapy

QUESTION: Dr. Woods, will you evaluate autogenous vaccine therapy in ophthalmology?

DR. ALAN C. WOODS, Baltimore: Autogenous vaccine therapy should be, theoretically, a highly specific form of treatment, based on the premise that the organism concerned is causally related in some manner to the ocular disease. The difficulty of establishing such a premise is obvious. Simple cutaneous reactivity to the organism means little, for most persons are more or less sensitive cutaneously to organisms which they habitually harbor or to which they are constantly exposed throughout life. But if this premise can be reasonably established by clinical observation, demonstration of undue hypersensitivity, focal reactions or some other means, and if, further, the antigenic properties of the organism are known and considered in the preparation of the vaccine, and if the proper method of administration is established, then autogenous vaccine therapy may be a worth while procedure. Circumstances in which it would be valuable are (*a*) the presence of chronic staphylococcic conjunctivitis, the isolation of a toxin-forming hemolytic staphylococcus from the conjunctiva, the demonstration of undue cutaneous sensitivity to the toxin and the intracutaneous administration of the toxin, or (*b*) the presence of recurrent acute iritis associated with rheumatoid arthritis, the isolation of a pathogenic streptococcus from a focus of infection, the demonstration of undue cutaneous sensitivity to the nucleoprotein fraction, the preparation of a vaccine from the bacterial body and its intravenous administration.

On the other hand, the random selection of certain or all of the organisms from the nasal or intestinal flora, the assumption that such organisms are related to the ocular disorder on the little information that the patient shows some cutaneous reactivity to them, the preparation of a vaccine without any especial regard to the hapten, nucleoprotein or exotoxin fraction and routine subcutaneous administration constitute, to my mind, little more than old-fashioned shotgun therapy. If any beneficial effects are observed, they are more likely to be nonspecific than specific.

DR. SANFORD R. GIFFORD, Chicago: Is there any a priori reason to think that there is sense in local vaccine therapy, for instance, use of staphylococcus toxoid in the treatment of staphylococcic conjunctivitis when a toxin-forming staphylococcus has been demonstrated? I think I have had some good results from local use of such toxoid in increasing dilutions.

DR. ALAN C. WOODS, Baltimore: I have never used toxoid directly in the eye but have used it cutaneously, starting with a low strength.

DR. SANFORD R. GIFFORD, Chicago: I am asking Dr. Woods as an expert in immunotherapy whether it is possible for a local immunity to take place that way.

DR. ALAN C. WOODS, Baltimore: I should think the vaccine might have to be given subconjunctivally, but I have had no experience with either method.

QUESTION: How would you evaluate nonspecific vaccine therapy, Dr. Woods?

DR. ALAN C. WOODS, Baltimore: Do you mean nonspecific protein therapy or the use of preparations one buys in a drugstore, vaccines for colds and coughs?

DR. DANIEL B. KIRBY: Typhoid vaccine, etc.

DR. ALAN C. WOODS, Baltimore: I think there is a tremendous use for nonspecific protein therapy. There is a great deal of evidence that a person undergoes a definite biologic reorientation after such therapy: a local mobilization of anti-

bodies, a decrease in sensitivity, changes in the reticuloendothelial system and changes in the vegetative nervous system. The changes are accompanied by a positive phase, with an exacerbation of the local lesion, and then by a negative phase, with a decrease in the local inflammation. I think the effect is purely nonspecific, and the question of whether it is due to the leukocytosis or to the mobilization of antibodies, etc., has never been solved. I am, however, firmly convinced that nonspecific protein therapy is of value in ophthalmology.

Sympathetic Ophthalmia

QUESTION: Dr. Woods, will you describe the present status of desensitization with uveal pigment for sympathetic ophthalmia?

DR. ALAN C. WOODS, Baltimore: In evaluating desensitization with uveal pigment for sympathetic ophthalmia, I think one must consider two things: first, the reason pigment is used and, second, the stage of the disease at which such treatment is instituted. Approximately 95 per cent of patients with sympathetic ophthalmia show positive cutaneous reactions to uveal pigment in the early and active stages of the disease. The histologic picture in the injected skin is similar to the picture in the eye—epithelioid and round cell infiltration with pigment phagocytosis. But patients with other conditions may show such positive reactions—post-traumatic uveitis and uveitis with dysacousia, alopecia and poliosis. The most definite statement that can be made about uveal pigment at the present time is that it apparently sets the stage for sympathetic ophthalmia and determines the histologic picture. Something else probably touches off the fire after the stage is set. Therefore, all one can hope to accomplish by pigment desensitization is to remove one factor which appears to be an intrinsic part of the disease. The pigment is absorbed slowly, and while one can desensitize with it, desensitization is usually a long process. Secondly, sympathetic ophthalmia is characterized by a moderate inflammatory reaction and a massive cellular infiltration, which often produces irreparable organic damage to the eye. If pigment therapy is started early, before the cellular infiltration has caused organic damage, the results according to my experience are encouraging. The inflammatory phase appears shortened, and, correspondingly, the cellular infiltration and organic damage are less. But when pigment therapy is started late, after adhesions and capsular clouding of the lens have formed, then, even though the inflammation may be checked, the eye is still blind from the organic damage. However, I have observed that even when desensitization has been done late the eye seems to do better when subjected to operative procedures. I believe, therefore, that pigment desensitization if started early shortens the duration of the disease and lessens the residual damage, and if started late at best assists in terminating the inflammatory phase but has no effect on the organic damage already done or under way. But when done early or late, pigment desensitization seems to render an eye affected by sympathetic ophthalmia a much better operative risk.

QUESTION: Dr. Woods, will you explain the effect on ocular tuberculosis of (*a*) sulfonamide compounds, (*b*) foreign protein, (*c*) blood injected into the anterior chamber and (*d*) roentgen rays?

DR. ALAN C. WOODS, Baltimore: A. Chemotherapy with the sulfonamide compounds has been completely disappointing in the treatment of ocular tuberculosis. There is experimental evidence that such therapy in guinea pigs prior to and after inoculation inhibits the development of disseminated tuberculosis. Stimulated by this observation, I have treated patients with active tuberculous uveitis and scleritis with sulfonamide drugs, keeping the concentration in the blood up to 8 mg. per hundred cubic centimeters for two weeks or longer. I have observed not the slightest therapeutic response.

B. I believe that foreign protein therapy is often of distinct value in the acute inflammatory phases of the lesion, especially in early exudative choroiditis,

in which after three or four bouts of nonspecific therapy, the lesions frequently become circumscribed and subside. I usually employ such nonspecific therapy before beginning tuberculin therapy.

C. I do not believe that injections of the patient's own blood into the anterior chamber are any more valuable than simple paracentesis and drainage of the aqueous. The second aqueous has always an increased antibody content, which is the reason usually accepted for the well known therapeutic effect. I have used such injections after paracentesis, but since they did not appear to add to the good results and were accompanied with a slight additional danger of ocular trauma and infection, I have abandoned their use.

D. My experience with roentgen rays and the gamma rays of radium in the treatment of ocular tuberculosis has been neither extensive nor encouraging. After the report of Kumer and Sallmann, I used these rays in several cases. There was usually a mild to moderate reaction, or primary positive phase, and only rarely the beneficial negative, or secondary, phase. Besides, both roentgen rays and gamma rays carry with them the danger of later damage to the lens. I have abandoned these rays entirely in favor of the beta rays of radium. The latter penetrate only 2 to 3 mm., carry with them no danger of damage to the lens, rarely cause any primary reaction and, according to my experience, have a definite therapeutic effect in anterior ocular tuberculosis.

Iritis

QUESTION: Dr. Adler, how do you handle recurrent iritis of undetermined causation?

DR. FRANCIS HEED ADLER, Philadelphia: My method is fever therapy with typhoid vaccine and administration of a sulfonamide compound simultaneously, managed so that the full concentration of the drug is in the blood stream at the height of the fever. After the patient is discharged from the hospital, sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) is given, 1 Gm. twice a day.

If posterior synechias form, a basal iridectomy is done as early as possible. Otherwise repeated synechias may cause complete seclusion of the pupil, with resultant secondary glaucoma.

QUESTION: Dr. Gifford, you stated that in treating uveitis or iritis with secondary glaucoma you sometimes stop giving atropine sulfate and substitute a mild miotic. If the atropine sulfate cannot be neutralized, and the effect continues for a week or more, how do you accomplish anything within this period?

DR. SANFORD R. GIFFORD, Chicago: When a patient has had atropine given him or has complete paralysis of accommodation and complete internal ophthalmoplegia, one can reduce the pupil with pilocarpine for a time, and as soon as the effect of the pilocarpine wears off the pupil will dilate again. If one uses a mild miotic one frequently can make the pupil smaller than before. The only question is whether miotics ought to be used at all in the presence of active uveitis, and I try to use them only in cases in which there is posterior uveitis or in which active iritis is about to subside to the point where a miotic will not do any harm. One can contract the pupil in the presence of atropine and keep up the contraction until the effect of the atropine has worn off.

QUESTION: In the presence of active iritis or uveitis would Dr. Gifford or Dr. Adler think it advisable to use paracentesis for the purpose of obtaining specimens for clinical research?

DR. FRANCIS HEED ADLER, Philadelphia: In the three or four months I spent in Paris with Morax in 1921 I saw many normal persons who had their anterior chambers tapped, and I do not recall ever seeing damage result. However, I do not think it is fair to the patient to carry out the procedure without securing his consent, even though I do not believe any harm will result.

Miotics

QUESTION: Dr. Adler, do miotics affect visual acuity through any action on the retina?

DR. FRANCIS HEED ADLER, Philadelphia: Wessely claims that the vessels of the conjunctiva are definitely contracted by physostigmine and that the retinal vessels may be similarly affected. He has shown that shortly after physostigmine is instilled in the eye there is a diminution of sensitivity in the central portions of the field to small test objects, and that this may even amount to a temporary central scotoma.

The finding of earlier experimenters that physostigmine causes a definite increase in the protein content of the aqueous has been verified. Although this finding was interpreted by Seidel to indicate that the ciliary body was a gland and that the aqueous was formed by secretion, my co-workers and I showed that in a series of cats the same effect continued after the ciliary ganglion had been removed. Hence the increase in protein is probably due to some direct effect of the physostigmine on the blood vessels of the interior of the eye. All these changes suggest that physostigmine causes profound effects on the eye besides the well known contraction of the pupil.

DR. MARK J. SCHOENBERG: There is good evidence that pilocarpine can produce edema of the macular area. The following observation, made by Hess and published some twenty-three years ago, will explain what I have in mind: If while looking through a 1 mm. hole in a small black cardboard at an evenly illuminated bright area (the sky or a white shade in front of a lighted electric light bulb will do), one moves the card rapidly in a circular fashion in front of one eye (the other eye is closed), one sees a number of fine lines, small circles and small dots like pinpricks. These are capillaries and retinal elements in the observer's eye. If a drop of a 2 per cent solution of pilocarpine nitrate or chloride is instilled in that eye and the observation is repeated fifteen to twenty minutes later, the capillaries, "pinpricks" and circles do not appear. Instead, one sees a grayish blotch. After two hours the blotch begins to disappear and the capillaries, etc., reappear. I have tried this procedure on a number of my patients, and Dr. Fridenberg and I have experimented on ourselves to observe this interesting phenomenon. I believe that Hess's observation is correct and that pilocarpine produces in some cases edema of the macular area. If this is so, should one not be more careful in using it in the treatment of glaucoma, at least as far as the frequency of instillations is concerned?

DR. PERCY FRIDENBERG: In the Hess entoptic phenomenon which Dr. Schoenberg has described, I see snaky lines at the periphery of the area. Inside of this area are little circles, none of them colored, and all these structures are double refracting and definitely without color. Dr. Schoenberg asks his patients to describe (*a*) the snaky lines, (*b*) the disks or bubbles and (*c*) the pinpoints. The central area is a clear, transparent, horizontal oval, from which the pinpoints, closely spaced, radiate in a star form. The snaky lines are obviously capillaries, and they do not run, like fingers, straight down from above or up from below, but weave in the general direction of, and some come rather close to, the central area. The radiating figure, I think, is an indication of Müller's supporting fibers, which present the "star" at the macula when pathologically altered (sclerosis, lipoid?) in retinitis. The disks may be the footplates of the recipient elements. When the stenopaic stop is held motionless, one sees only the opacities in one's own vitreous, if there are any, and no trace of the foveal pattern described. However, they disappear as soon as the stop is moved rapidly to and fro or, preferably, in a circular path.

QUESTION: Dr. Schoenberg, have you any adjuvants to the miotics in the treatment of glaucoma?

DR. MARK J. SCHOENBERG: Yes, there are a number of valuable adjuvants. Most patients listen attentively to and follow the physician's instruction. Patients

should be given printed or, better yet, typed instructions as to what to avoid doing and what to do. These instructions should advise eating the proper food, getting regular sleep, spending a certain time outdoors, observing the principles of mental hygiene, etc. Everything that contributes to the maintenance of good health should be promoted without one's asking the impossible of the patient.

Superficial Punctate Keratitis; Keratoconjunctivitis

QUESTION: Dr. Gifford, what do you find to be the best treatment for superficial punctate keratitis, and how do you treat epidemic keratoconjunctivitis?

DR. SANFORD R. GIFFORD, Chicago: When individual lesions in superficial punctate keratitis are large enough to be seen grossly I touch each one as it appears with pure trichloroacetic acid on a fine cotton point. One may do this with some very small lesions under slit lamp illumination, removing the microscope head and using the loupe. A saturated solution of iodine may also be used (5 minims [0.3 cc.] each of tincture of iodine and glycerin and 5 grains [0.3 Gm.] of powdered iodine crystals.)

The conjunctivitis usually present is treated with Cowan's solution, 2 per cent potassium iodide solution with 2 drops of compound solution of iodine U. S. P. to the ounce (30 cc.). This may help to prevent new corneal lesions. I have not used Cowan's packs with Pregl's iodine solution. I have been afraid of damage to the corneal epithelium.

The eye is kept covered, if possible.

In cases of obstinate keratitis with repeated small infiltrates, two to three small doses (60 r) of roentgen rays unfiltered but carefully measured, are given. This treatment has seemed to stop prolonged keratitis in some cases.

A Schirmer test is done in such cases, and in a few lacrimal deficiency has been shown. In these cases Rucker's formula of 0.7 per cent gelatin in Locke's solution, with 0.5 per cent chlorobutanol as a preservative, is used six times a day.

A rhinologic examination is advised, and a few cases have been noted in which the mucosa was swollen and shrinking and cocainizing it has helped.

I have used vitamin A, but not with enthusiasm, and not locally.

A few peculiar cases have been observed in which marginal punctate infiltrates fused to form a ring infiltrate. In these cases keratotomy has saved the day. In one case keratotomy was performed in each eye, the interval being six months, with good results; the incisions were reopened daily for four to six days.

In epidemic keratoconjunctivitis, I use Cowan's solution, but not with much confidence. I have not had convalescent serum available. I have used the roentgen ray treatment I have described for obstinate corneal lesions. The conjunctival sac should be kept clean and an iced glove used when the swelling is severe.

DR. DANIEL B. KIRBY: Dr. Braley at last month's meeting was somewhat pessimistic about treatment. Has he any reason to change his position?

DR. ALSON E. BRALEY: I have given convalescent plasma in 25 cases with 3 failures. In all the cases the condition was proved by the development of neutralized antibodies to the virus, and I feel that this treatment is of some value. When the condition is severe a good deal of plasma must be administered. As much as 150 cc. of sodium sulfathiazole solution has no effect on the disease.

DR. DANIEL B. KIRBY: I think it would be well if Dr. Braley would tell how to collect the serum and whether individual units may develop their own serum banks.

DR. ALSON E. BRALEY: Convalescent serum is easily obtained from a patient who has recovered from the disease. However, I determine when the patient has the highest degree of immunity by intracerebral inoculations of mixtures of virus with the patient's plasma or serum. This gives an indication as to the number of neutralizing antibodies present; I like to draw the blood when there are at least 10,000. In other words, the patient's serum will protect against 10,000 doses of the virus when injected intracerebrally into mice. My associates

and I are trying now to work out a precipitin reaction which will not take so much time and so many mice, but at present the method described is the only one available. The number of neutralizing antibodies is usually highest from sixty to ninety days after the patient recovers from the disease, but the peak varies in individual cases. It may occur forty days after recovery. Some persons carry their immunity for a year, and others lose it rapidly; we therefore draw the blood as one would for a blood bank, having at least 9 persons to draw it from. The plasma, which should represent all the blood groups, is pooled, placed in 50 cc. ampules, frozen in a carbon dioxide ice box and kept there for two weeks while being tested for sterility. It is then released for use, and is given intravenously in 50 cc. lots. I do not know whether the intravenous is the best route. I now have some patients who are getting the plasma intravenously and others who are getting it locally. I have tried 50 cc. and 150 cc., and have given 3 patients normal plasma. It has been difficult to choose patients to be given normal plasma except at random.

DR. SANFORD R. GIFFORD, Chicago: I should like to ask Dr. Braley what his criterion of success is. Is he able to prevent the corneal lesions from appearing, or does he simply shorten the course of the disease? I have observed a number of cases of apparently mild keratitis and a few cases in which the corneal lesions definitely did not appear. I meant to speak of convalescent serum, but none has been available in Chicago.

DR. ALSON E. BRALEY: The criterion for success is twofold. The prevention of corneal lesions is the principal consideration; a large number of patients who have mild corneal lesions will have corneal opacities if left alone. The second criterion is shortening of the morbidity period to from two to six days.

DR. ALAN C. WOODS, Baltimore: Are retrobulbar injections of alcohol used to cut down the sensitivity?

DR. SANFORD R. GIFFORD, Chicago: I have not used them. I use ice, and it works fairly well.

DR. ALSON E. BRALEY: I do not use injections of alcohol.

Treatment of Epiphora

QUESTION: Dr. Gifford, how do you treat epiphora with patent ducts and no visible local pathologic change?

DR. SANFORD R. GIFFORD, Chicago: This is a rare condition as described in the question. I have seldom seen it. One patient had a brain tumor with irritation of the fifth nerve. The epiphora was relieved slightly by use of local anesthetics and wearing of protective glasses or goggles. I use 1 per cent procaine hydrochloride with 1:4,000 epinephrine hydrochloride solution.

A few patients have ducts which can be washed through, but not easily. These may be helped by an occasional probing; a drop of 10 per cent cocaine hydrochloride solution can be washed through first, and if this procedure is repeated once or twice, after five minutes probing is painless, or practically so.

The more common condition is that in which a local pathologic condition is really present but is not visible to some observers. The condition I mean is due to stenosis or displacement of the puncta. Displacement is easily seen; stenosis, much less so. It is necessary to try the lower punctum delicately with a dilator. If it is small or tight, as it frequently becomes in middle-aged or elderly persons, relief is obtained by careful enlargement. It is not enough to stretch the punctum. It must be permanently enlarged just enough and made to dip into the lake of tears by right-angled incisions. Ten per cent cocaine hydrochloride solution on a fine film of cotton over the punctum for five minutes induces sufficient anesthesia. The scissors used must be fine and shown to be very sharp by being tried on cotton. A 2 mm. cut is made along the canaliculus and another straight in from the punctum, going through its floor. These are kept open daily for four or five days, or until they stay open spontaneously.

DR. ERNST WALDSTEIN: I should like to ask Dr. Gifford whether he has ever tried roentgen irradiation to the lacrimal gland. This method, tried in former years, has seemed to work in certain cases.

DR. SANFORD R. GIFFORD, Chicago: I have never used roentgen rays because I am afraid of producing keratoconjunctivitis sicca, which is a much severer condition than epiphora. I would rather not run the risk of producing dryness of the eye.

Diabetic Retinopathy

QUESTION: Dr. Adler, do you know of any treatment that affects diabetic retinopathy?

DR. FRANCIS HEED ADLER, Philadelphia: At the present time the answer is no. Diabetic retinopathy is becoming a more and more important problem for the ophthalmologist. Since the advent of insulin and a more thorough knowledge of the metabolism of the body in diabetes, diabetic patients are living longer. It is now recognized that the key factor in the development of diabetic retinopathy is time. No longer can one say that retinopathy develops only in old persons with diabetes. One now sees it in the young patient with severe diabetes simply because he now lives long enough to acquire it, whereas formerly he died before it could occur.

Before one can adequately treat a condition, one must know what it is due to. As yet there is no certain knowledge as to the cause of diabetic retinopathy. It cannot be the level of the blood sugar, for the severest retinal changes occur in patients with relatively mild hyperglycemia, who average 150 to 170 mg. of sugar per hundred cubic centimeters of blood.

The incidence of diabetic retinopathy increases as the severity of retinal arteriosclerosis, but this does not mean that the retinal changes are directly due to the sclerosis. The two may be dependent on a common cause. Certainly the type of change in the eyegrounds is different from that produced by ordinary arteriosclerosis. Recently the venous portion of the circulation has been incriminated, but changes there apparently are not found in all diabetic patients with retinopathy.

Capillary fragility due to vitamin deficiency has been thought to be the cause of the hemorrhages, and Friedenwald at first thought his patients were benefited by administration of ascorbic acid and vitamin B complex. Later he failed to confirm this opinion. Yudkin reported benefit from lemon juice, and Szent-Györgyi stated that citrin, or vitamin P, is the antifragility factor and that this factor is absent from synthetic vitamin C but present in fruit juices.

Burch has reported benefit from vitamin K in hemorrhagic retinitis, but this vitamin is known to be effective only when there is an increase in prothrombin time, and it is not likely that this increase is present in all patients with diabetic retinopathy.

In recent years attention has been centered on fat metabolism. It is now known that in diabetic patients any excess of fat is not burned completely but is deposited in the liver and probably in the walls of the blood vessels as well. In dogs there is a parallelism between the development of fat in the liver and arteriosclerosis. It is possible, therefore, that this knowledge of the further changes in metabolism may eventually be of value in preventing retinopathy. I still know of no drugs which either prevent or ameliorate diabetic retinopathy.

Vitamin Therapy in Ocular Conditions

QUESTION: Dr. Gifford, will you generalize briefly as to your experiences with vitamin therapy in ocular conditions?

DR. SANFORD R. GIFFORD, Chicago: First, as to vitamin A: Keratomalacia is rare according to my experience. I have seen no case like that of Dr. Schlivek. There is a tendency to use vitamin A in the treatment of any obstinate corneal

ulceration, but my experience with it in such cases is not convincing. It should be given to old or feeble persons with ulcers, especially recurrent catarrhal ulcers. In treating keratoconjunctivitis sicca I always use it. Also, it apparently should be used for the mild form of epithelial dystrophy. There are a few apparent results in asthenopia (Cordes and Harrington), which are not convincing. I believe night blindness due to vitamin A deficiency is really rare, but one can hardly refuse vitamin A to persons who think they are night blind. I believe DeRoetth has proved that there is no indication for using it locally.

With vitamin B_1, thiamine hydrochloride, I have had the same results as Carroll in toxic amblyopia. I have had apparently good results in retrobulbar neuritis, as good as those in a series of Duggan's, but one must allow for the tendency to spontaneous recovery in this disease. I have had a few elderly patients, with loss of vision, including 2 in whom it occurred after cataract extraction and there were field defects indicating nerve damage. One had mild cirrhosis of the liver and made good progress with thiamine hydrochloride. He is still taking it and has maintained good vision.

With vitamin B_2, riboflavin, I have had good results in rosacea keratitis, using 5 to 10 mg. a day. I have also given it to a few patients with corneal lesions resembling rosacea. One patient with severe phlyctenulosis improved.

Vitamin C, cevitamic acid, I have used before intraocular operations and have had few hemorrhages, but I am not convinced of its value. I use 100 mg. a day for a few days before and one week after operation. I also use it with vitamin B complex in treating diabetic retinopathy, probably without beneficial results.

Vitamin D, in combination with vitamin A, I have used in treating phlyctenulosis and severe blepharitis in children.

Vitamin B complex has been used as a follow-up in treating nerve lesions and rosacea keratitis. The nicotinic acid which is part of the B complex acts as a vasodilator.

As to vitamin P, or citrin, I am trying hesperidin in doses of 1.5 Gm. a day for diabetic retinopathy. Theoretically, this should be of value; its use is certainly more logical than vitamin C and vitamin B complex.

Vitamin K has few indications in ophthalmology. It may prevent hemorrhages of the newborn, but only if the prothrombin clotting time is prolonged.

Vernal Catarrh

QUESTION: Dr. Schoenberg, how do you handle vernal catarrh?

DR. MARK J. SCHOENBERG: The patient is advised to go if possible to a drier, cooler climate during the hot, sunny, damp summer months. Butyn sulfate in 0.25 to 0.5 per cent solution is instilled in each eye two to four times a day (according to how hot the day happens to be); this is followed by application of cold (35 to 45 F.) for ten to fifteen minutes; 2 drops of epinephrine hydrochloride in 1/10,000 solution is then instilled. The patient should wear dark blue glasses, keep out of the sunlight as much as possible and avoid the seashore.

Primary Atrophy of the Optic Nerve

QUESTION: Dr. Woods, what do you think is the best therapeutic approach to syphilitic optic nerve atrophy?

DR. ALAN C. WOODS, Baltimore: In my opinion, the only possible therapeutic approach to the primary optic nerve atrophy of late acquired syphilis is fever therapy. If the condition is not treated the end result is total blindness in from seven to nine years. With ordinary routine treatment the results are little, if any, better. Intracisternal treatment with arsphenamized serum offers a better general prognosis, but since this form of treatment carries with it the danger of sudden extinguishment of vision, it is excluded. Fever therapy should be followed by adequate routine therapy. Tryparsamide is the one arsenical that must be excluded.

I say this not because I believe tryparsamide has any specific harmful effect on the partially atrophied optic nerve, but because one should not expose an already damaged optic nerve to the risk of additional trauma.

Malaria is the only mode of fever therapy with which I have had any experience. It may be that other forms are equally efficacious, but there is no available information that this is so. The present figures indicate that the process in the nerves is arrested if blindness does not occur in the first three years after the fever therapy. In actual practice the patient is inoculated with benign tertian malaria (patient to patient transfer). From ten to fourteen paroxysms are usually permitted; then quinine is given, and thereafter routine treatment with arsphenamine or neoarsphenamine is carried out.

QUESTION: Where is the lesion in optic nerve atrophy, in the retina or in the nerve itself?

DR. ALAN C. WOODS, Baltimore: I assume the question means the optic nerve atrophy of dementia paralytica and not that of chronic meningovascular neurosyphilis. The site of the lesion in tabes usually lies in the anterior portion of the nerve.

Heparin and Dicoumarin

QUESTION: Dr. Adler, what experiences have you had with heparin and dicoumarin (3,3′-methylenebis-[4-hydroxycoumarin])?

DR. FRANCIS HEED ADLER, Philadelphia: My associates and I routinely use heparin and dicoumarin in all cases of obstruction of the retinal circulation, whether arterial or venous. I have seen only 1 patient in whom heparin was of possible benefit in arterial obstruction, and I could not swear that he might not have recovered without the use of this drug, as he was given nitrites in addition. He had closure of one of the branches of the inferior retinal artery. Treatment was started within several hours after the initial symptoms had begun. The patient had only one eye. The ophthalmoscopic appearance was typical, and the closed vessel opened up after several hours of treatment.

From 3,500 to 4,000 Toronto units of heparin is administered intravenously as an initial dose. At the same time, 5,000 Toronto units is given intramuscularly. Subsequent doses are controlled by frequent determinations of the clotting time with the object of keeping the clotting time as determined by the Lee-White method between thirty and sixty minutes. (EDITORIAL NOTE: The editors feel that a word of warning should be given to those not experienced in the use of heparin.) Dicoumarin is administered orally as an adjuvant; 300 mg. is given the first day of treatment and 200 the second. Thereafter the doses are controlled by determination of the prothrombin concentration with the aim of maintaining a level of between 15 and 20 per cent. Therapy is continued for about two weeks. With long-continued therapy there seems to be an increase in the danger of the hemorrhagic phenomenon at this level.

There are at least two types of obstruction in the venous portion of the retinal circulation. The one type is probably due to phlebosclerosis which accompanies arteriosclerosis, and, owing to the fact that the retinal arteries and veins have a common adventitial sheath at the crossings, the sclerotic process in the arteries spreads up and down the veins. This type occurs in elderly persons and is nearly always found in the central vein, or, when a branch is affected, it is usually the superior temporal, and the obstruction begins at an arteriovenous crossing. In my experience this type of obstruction has never benefited from the use of heparin or vasodilator drugs, paracentesis, roentgen irradiation or anything else.

The other type occurs in younger persons and is an entirely different disease. It is an inflammatory condition, a periphlebitis, the cause of which is usually tuberculosis. Only a branch of the vein is involved in most cases, and the prognosis is relatively good. Recovery is spontaneous, which fact may account for some of the favorable reports in the literature on the use of heparin.

I have had 2 patients with such obstruction, one a young girl who several years previously had had a kidney removed, which was found to be definitely tuberculous, and the other a woman of 38 who had had pulmonary tuberculosis in her twenties. The young girl was not given heparin by me; the other patient was seen in consultation and heparin was given by the attending physician. Both recovered completely, with full fields and full visual acuity.

So far, I have had no cause to regret using heparin, but the day may come when some one with high blood pressure and arteriosclerosis will break a vessel while he is being heparinized. On the other hand, it is the logical remedy and if used early enough may do some good.

DR. DANIEL B. KIRBY: Dr. Paton has had some experience with these drugs; perhaps he will describe his results.

DR. R. TOWNLEY PATON: Experimental results with the use of heparin have not been encouraging thus far. I would say, however, that heparin is of no particular value unless used immediately after the occurrence of the thrombosis. I have noted some good results in the treatment of spasm of the retinal vessels. Conclusions, however, cannot as yet be reported, because of an insufficient number of cases.

Recurrent Corneal Erosion

QUESTION: Dr. Gifford, will you discuss your treatment of recurrent corneal erosion?

DR. SANFORD R. GIFFORD, Chicago: I am glad I was asked this question for the reason that I do see patients in Chicago in whom the condition either has not been diagnosed correctly or has been treated with temporizing measures which have allowed it to keep recurring, when according to my experience the treatment is relatively simple. I mean really recurrent erosions; I do not mean a simple erosion which heals up spontaneously. When the area of loose epithelium is small and is seen soon after injury, one may use 20 per cent trichloroacetic acid and apply a monocular dressing, which is not to be removed for four days. But if the loose area is large, or a number of recurrences have taken place, temporizing, in my opinion, is a waste of time. I believe the only method to use is the radical one, which consists of removing all loose epithelium, often almost to the limbus all around. Apply 10 or 15 per cent trichloroacetic acid to the whole denuded area, wiping it on with a small hard cotton applicator. This turns the surface a faint gray, but leaves no scar. Use butyn sulfate (2 per cent) and metaphen (1:3,000) ophthalmic ointment. Apply a binocular dressing, which is not to be removed for four days. Follow by a monocular dressing for two or three days. Oil is used for dressing the affected eye, which need not be done until the seventh day. Use oil and then no treatment, or use oil in the eye at night. I use olive oil.

In a few cases of old erosion or erosion following ulcer or inflammation, including postoperative iritis, the condition resists this treatment. It should then be repeated and followed immediately with formation of a large intermarginal adhesion by Wheeler's method. This is left in for three months.

In 1 case an erosion of long standing (over a year) resisted these forms of treatment and healed under a complete conjunctival flap, removed after six months.

For very small staining areas at the site of a small scar in the epithelium, use oil in the sac at night and 1 per cent ethylmorphine hydrochloride three times a day.

Book Reviews

Flying Men and Medicine. By E. Osmun Barr, M.D. Price, $2.50. Pp. 254. New York: Funk & Wagnalls Company, 1943.

This book is a prospectus for prospective fliers. It is an extremely elementary (high school level) discussion of aviation medicine directed toward youngsters who want to fly. It has no place in an ophthalmologic library. It has a place in a public library or in a high school library, so that those innocent of all knowledge of physiology can with a minimum of effort learn some first elements. It takes its place among the large number of simply written books prepared for lay consumption.

The book consists of an introduction, a foreword and a preface followed by two general divisions, the first considering the "nervous system and contributing parts" and the second dealing with the "other systems of the body." There follows an index. This structure should not be misconstrued as indicating the volume to be a textbook. The author frankly calls it a "story," or a "narrative."

Oversimplification is its chief defect. This leads the author into misstatements such as that of labeling the anterior chamber the "frontal chamber" and the vitreous the "back chamber" in a diagram of the eye and stating that both are filled with "fluid," and repeating the statement that there are normally about 5,000,000 red cells in the blood. He makes a similar erroneous statement concerning the white blood cells. As a physician he knows better, but he has not been careful enough in these instances, as in numerous others, to avoid planting misconceptions in his lay reader's mind.

The book has value only in indicating to the prospective young flier the necessity for careful medical examination and supervision of fliers and the extra physical, mental and emotional hazards encountered in modern flying.

LeGrand H. Hardy.

Nicholas Copernicus, 1543-1943. By Stephen P. Mizwa, A.M., LL.D Unbound. Complimentary. Pp. 88. New York: The Kosciusko Foundation, 1943.

This sumptuous brochure is not only a commemorative biography of the Sarmatic astronomer who was greeted by Melanchthon as the man who made the world move and bade the sun stand still and thus revolutionized the concept of the solar system. Nor is it just the life story of one who was distinguished as a statesman, soldier and physician. Beautifully illustrated and authoritatively documented, literally as well as figuratively, with a wealth of drawings, reproductions of old maps, manuscripts, historical monuments, paintings, music and costumes, it gives a remarkable picture of an era when there was an almost unprecedented exchange in science, letters and art and in sociopolitical and philosophic thinking throughout Europe, a period in which the homeland of Copernicus played a by no means unimportant role. The cover design in color, by the well known artist Arthur Szyk, is a symbolic portrait of the astronomer with a host of his academic and scientific attributes and insignia. The end paper is a map of the copernican solar system. This quadricentennial tribute will be read with interest by the historically minded and looked over again and again by all who appreciate an admirable piece of bookmaking as well as a worthy tribute to a great figure in the history of science and of Poland.

Percy Fridenberg.